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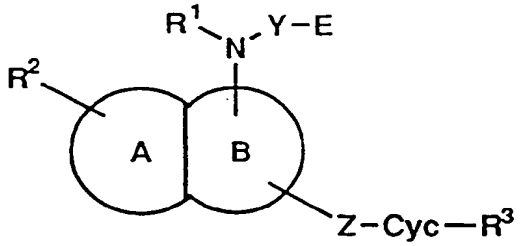
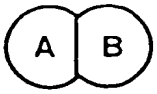
(54) Heterocyclic compounds

(57) The compounds of the formula:



(I)

wherein



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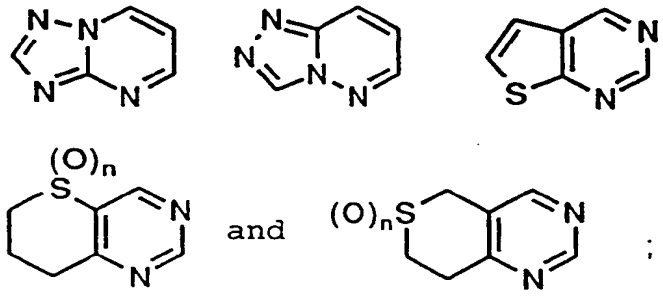
is a heterocycle selected from



n is 0, 1 or 2;
Y is bond or alkylene;
Z is bond, alkylene or vinylene;
E is

(i) 4-15 membered, unsaturated, partially saturated or fully saturated, mono or bicyclic hetero ring containing one or two hetero atoms, chosen from nitrogen, oxygen and sulfur, not more than one hetero atom being sulfur,
(ii) 4-15 membered, unsaturated or partially saturated, mono or bicyclic carbocyclic ring, or
(iii) $-OR^4$ (in which R^4 is hydrogen atom, alkyl or alkyl substituted by a hydroxy group);
Cyc is 5-7 membered, unsaturated, partially saturated or fully saturated, monocyclic hetero ring containing one or two nitrogen atoms or 5-7 membered, unsaturated or partially saturated, monocyclic carbocyclic ring;
R^1 is H or alkyl;
R^2 is H, alkyl, alkoxy or halogen atom;
R^3 is H, alkyl, alkoxy or $-COOR^5$ (in which R^5 is H or alkyl);
with the proviso that

(1) a Cyc ring does not bond to Z through a nitrogen atom in the Cyc ring when Z is vinylene and that
(2) Y is not a single bond, when E is $-OR^4$;
and pharmaceutically acceptable acid addition salts, pharmaceutically acceptable salts and hydrates thereof have inhibitory effect on cGMP-PDE, or additionally on TXA_2 synthetase.

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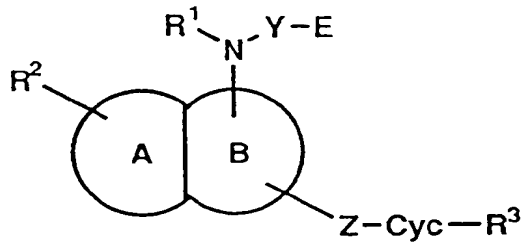
Description

The present invention relates to heterocyclic compounds and their preparation and use.
More particularly, this invention provides heterocyclic compounds of the formula (I):



(I)

wherein all symbols are as hereinafter defined, and pharmaceutically acceptable acid addition salts, pharmaceutically acceptable salts, and hydrates thereof, which are useful as inhibitors of cyclic guanosine 3', 5'-monophosphate phosphodiesterase, or additionally of thromboxane A_2 synthetase, and processes for their preparation, and their use.

Cyclic guanosine 3',5'-monophosphate (abbreviated as cGMP hereafter) was found in urine in rats by D. F. Ashman in 1963. Till now, it has been known that cGMP is distributed broadly in tissues of many animals including human beings. cGMP is biosynthesized from guanosine triphosphate (GTP) by the action of guanylate cyclase.

cGMP has been experimentally confirmed to have various physiological activities. For example, cGMP induces the relaxation of heart muscle and of smooth muscle. Further, it is related to the formation of neuronal synapses and it acts as a trigger of cell proliferation and it induces the proliferation of lymphocyte.

cGMP is metabolized to physiologically inactive 5'-GMP by the action of cGMP phosphodiesterase (abbreviated as cGMP-PDE hereafter).

Accordingly, the inhibition of the action of cGMP-PDE is considered to be useful for the prevention and/or treatment of diseases induced by enhancement of the metabolism of cGMP, such as hypertension, heart failure, myocardial infarction, angina, atherosclerosis, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, asthma, bronchitis, dementia, immunodeficiency, pulmonary hypertension.

On the other hand, thromboxane A_2 (abbreviated as TXA_2 hereafter) was found as a constituent of the arachidonate cascade, in platelets by M. Hamberg in 1975. TXA_2 is biosynthesized from arachidonic acid released from cell membrane via prostaglandin G_2 and prostaglandin H_2, and rapidly metabolized to inactive thromboxane B_2. TXA_2 is known to induce platelet aggregation and to contract smooth muscle, particularly blood vessel muscle and bronchial muscle. TXA_2 synthetase was isolated and purified from microsome in platelets.

Accordingly, the inhibition of TXA_2 synthetase decreases the biosynthesis of TXA_2, and is useful for the prevention and/or treatment of inflammation, hypertension, thrombosis, arteriosclerosis, cerebral apoplexy, asthma, myocardial infarction, cardiostenosis, cerebral infarction, etc.

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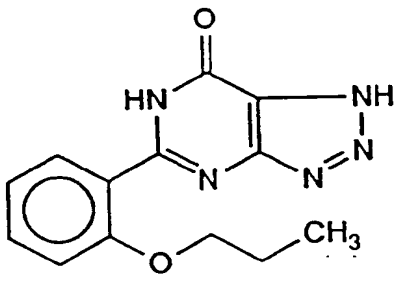
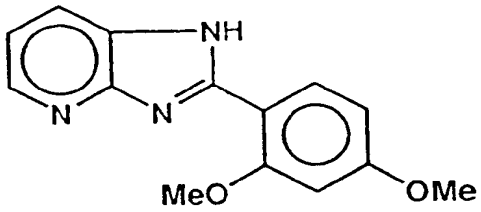
Up to now, some compounds have been known as cGMP-PDE inhibitors, for example,

Zaprinast



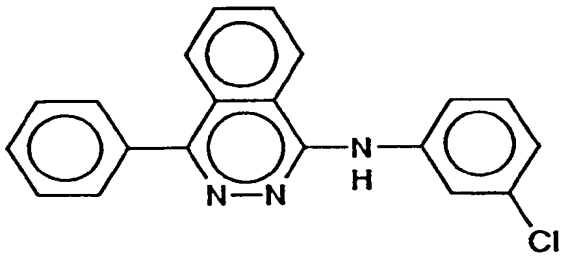
(A)

AR-L 57



(B)

MY-5445



(C)

Many compounds derived from the above lead compounds have been proposed and many patent applications relating to those have been filed. For example, as derivatives of Zaprinast, compounds wherein the 1H-1,2,3-triazole skeleton is replaced by various other hetero cycles (see USP-5047404), those wherein the triazole is replaced by a benzene ring (see EP-371731), and those wherein the triazole is eliminated, i.e. those having only the pyrimidine skeleton (see EP-395328), have been proposed. The above mentioned compounds always contain an oxo group at the 4th position of the pyrimidine skeleton. The compounds having an amino group at the said position are described in USP-4060615. The specification discloses 4-amino-6,7-dimethoxy-2-piperazinylquinazoline derivatives of the following formula:

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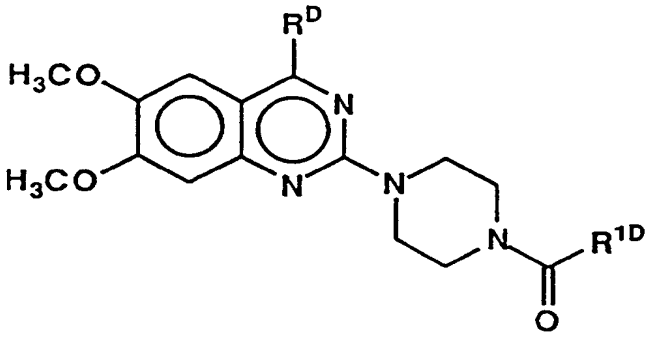
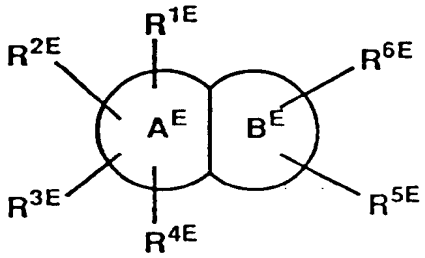


(D)

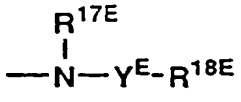
wherein R^D is amino or hydrazino,
R^{1D} is C3-8 cycloalkyl, C3-8 methylcycloalkyl or C4-8 cycloalkenyl, and their acid addition salts.

Recently, quinazoline derivatives having inhibitory activity on cGMP-PDE have been published (see WO 93/07124). In this specification, the quinazoline derivatives of the following formula are disclosed:



(E)

wherein ring A^E is benzene, pyridine or cyclohexane ring;
ring B^E is pyridine, pyrimidine or imidazole ring;
R^{1E}, R^{2E}, R^{3E} and R^{4E} are each, for example, hydrogen, halogen, lower alkyl optionally substituted by halogen, lower alkoxy, hydroxyalkyl, nitro, cyano, acylamino, optionally protected COOH, $S(O)n^E$-R^{7E} (n^E is 0,1,2, R^{7E} is lower alkyl), $NR^{45E}R^{46E}$ (R^{45E} and R^{46E} are each, for example, hydrogen, lower alkyl);
R^{5E} is, for example, optionally substituted heteroaryl (for example, pyridinyl, imidazolidinyl, quinazolidinyl);
R^{6E} is, for example,

(1) 

(R^{17E} is, for example, hydrogen, lower alkyl, alkoxyalkyl, hydroxyalkyl; Y^E is, for example, $(CN_2)q^E$ (q^E is 0 to 8); R^{18E} is, for example, hydrogen, hydroxy, optionally substituted heteroaryl, optionally substituted cycloalkyl),

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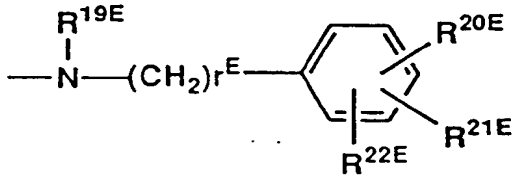
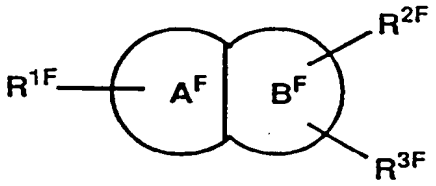
(2) 

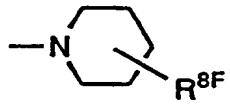
(R^{19E} is, for example, hydrogen, lower alkyl; R^{20E}, R^{21E} and R^{22E} are each, for example, hydrogen, halogen, nitro, low alkyl, alkoxy; r^E is 0 to 8); and pharmacologically acceptable salts thereof.

More recently, nitrogenous fused-heterocyclic derivatives having inhibitory activity on cGMP-PDE have been published (see WO 94/22855). In this specification, the nitrogenous fused-heterocyclic derivatives of the following formula are disclosed.

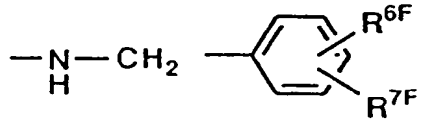


(F)

wherein ring A^F is benzene, pyridine or cyclohexane ring;
ring B^F is pyridine, imidazole or pyrimidine ring;
R^{1F} is $-NR^{4F}R^{5F}$ (wherein R^{4F} and R^{5F} are each, independently, hydrogen atom, lower alkyl, acyl group or a carbonyl group which may be protected, or alternatively R^{4F} and R^{5F} may form a ring together with the nitrogen atom to which they are bonded, provided that the ring may be substituted) or heteroaryl group which has one or two nitrogen atoms and may be substituted; R^{2F} is hydrogen atom, a group represented by the formula

(1) 

(wherein R^{8F} is a carboxyl or tetrazolyl group which may be protected), or a halogen atom;
R^{3F} is a hydrogen atom or a group represented by the formula

(2) 

(wherein R^{6F} and R^{7F} are each, independently, hydrogen or halogen atom or a lower alkyl group, or alternatively R^{6F} and R^{7F} may together form a methylenedioxy or ethylenedioxy group);
and pharmacologically acceptable salts thereof.

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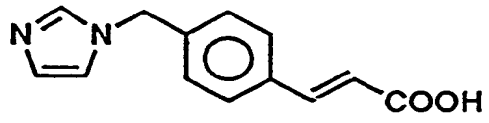
Furthermore, some TXA_2 synthetase inhibitors have been known, for example,

OKY-046



(G)

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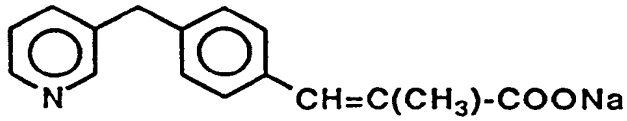
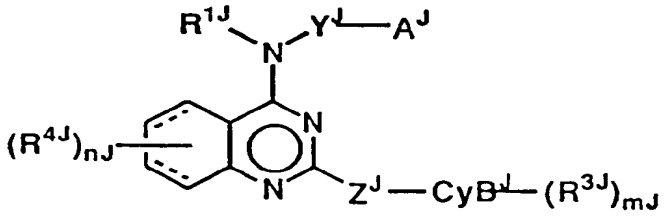


(H)

Many derivatives containing an imidazole or pyridine ring as the basic skeleton have been proposed.

Recently, quinazoline derivatives having an inhibitory effect on cGMP-PDE, or additionally on TXA_2 synthetase have been published (see EP-579496). In this specification, the quinazoline derivatives of the following formula are disclosed:



(J)

wherein R^{1J} is hydrogen or C1-4 alkyl;
Y^J is single bond or C1-6 alkylene;
A^J is (i) $-CyA^J-(R^{2J})l^J$,
(ii) $-O-R^{0J}$ or $-S(O)p^J-R^{0J}$ or
(iii) $-NR^{16J}R^{17J}$;
in which R^{0J} is hydrogen, C1-4 alkyl, hydroxy-C1-4 alkyl or $-CyA^J-(R^{2J})l^J$; R^{16J} and R^{17J} independently are hydrogen or C1-4 alkyl;
p^J is 0-2;
CyA^J is

(1) carbocyclic mono-ring of 3-7 membered, saturated or unsaturated,
(2) heterocyclic mono-ring of 4-7 membered containing one nitrogen, unsaturated or partially saturated,
(3) heterocyclic mono-ring of 4-7 membered containing one nitrogen and one oxygen, unsaturated or partially saturated,
(4) heterocyclic mono-ring of 4-7 membered containing one nitrogen and two oxygen, unsaturated or partially saturated,
(5) heterocyclic mono-ring of 4-7 membered containing two nitrogen and one oxygen, unsaturated or partially saturated,
(6) heterocyclic mono-ring of 4-7 membered containing one or two sulfur, unsaturated or partially saturated or
(7) heterocyclic mono-ring of 4-7 membered containing one or two oxygen, unsaturated, partially saturated or fully saturated;

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R^{2J} is (1) hydrogen, (2) C1-4 alkyl, (3) C1-4 alkoxy, (4) -$COOR^{5J}$, in which R^{5J} is hydrogen or C1-4 alkyl, (5) -$NR^{6J}R^{7J}$, in which R^{6J} and R^{7J} independently are hydrogen or C1-4 alkyl, (6) -$SO_2NR^{6J}R^{7J}$, in which R^{6J} and R^{7J} are as hereinbefore defined, (7) halogen, (8) trifluoromethyl, (9) nitro or (10) trifluoromethoxy;
Z^J is single bond, methylene, ethylene, vinylene or ethynylene; CyB^J is

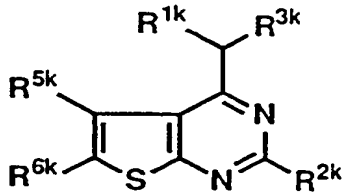
(1) heterocyclic mono-ring of 4-7 membered containing one nitrogen, unsaturated or partially saturated,
(2) heterocyclic mono-ring of 4-7 membered containing two nitrogen , unsaturated or partially saturated,
(3) heterocyclic mono-ring of 4-7 membered containing three nitrogen, unsaturated or partially saturated,
(4) heterocyclic mono-ring of 4-7 membered containing one or two oxygen, unsaturated or partially saturated, or
(5) heterocyclic mono-ring of 4-7 membered containing one or two sulfur, unsaturated or partially saturated;

R^{3J} is hydrogen, C1-4 alkyl, C1-4 alkoxy, halogen or trifluoromethyl;
R^{4J} is (1) hydrogen, (2) C1-4 alkyl, (3) C1-4 alkoxy, (4) -$COOR^{8J}$, in which R^{8J} is hydrogen or C1-4 alkyl, (5) -$NR^{9J}R^{10J}$, in which R^{9J} is hydrogen, C1-4 alkyl or phenyl(C1-4 alkyl) and R^{10J} is hydrogen or C1-4 alkyl, (6) -$NHCOR^{11J}$, in which R^{11J} is C1-4 alkyl, (7) -$NHSO_2R^{11J}$, in which R^{11J} is as hereinbefore defined, (8) $SO_2NR^{9J}R^{10J}$, in which R^{9J} and R^{10J} are as hereinbefore defined, (9) -$OCOR^{11J}$, in which R^{11J} is as hereinbefore defined, (10) halogen, (11) trifluoromethyl, (12) hydroxy, (13) nitro, (14) cyano, (15) -SO2N=CHN$R^{12J}R^{13J}$ in which R^{12J} is hydrogen or C1-4 alkyl and R^{13J} is C1-4 alkyl, (16) - $CONR^{14J}R^{15J}$ in which R^{14J} is hydrogen or C1-4 alkyl or phenyl(C1-4 alkyl) and R^{15J} is C1-4 alkyl or (17) C1-4 alkylthio, (18) C1-4 alkylsulfinyl, (19) C1-4 alkylsulfonyl, (20) ethynyl, (21) hydroxymethyl, (22) tri(C1-4 alkyl)silyl or (23) acetyl;
and l^J, m^J and n^J independently are 1 or 2; with the proviso that

(1) the group of the formula: -CyA^J-$(R^{2J})_l{}^J$ does not represent a cyclopentyl and trifluoromethylphenyl group when Y^J is a single bond, that
(2) a CyB^J ring should not bond to Z^J through a nitrogen atom in the CyB^J ring when Z^J is vinylene or ethynylene, that
(3) a CyB^J ring should not be pyridine or thiophene when CyA^J is a ring of CyA^J-(7) and that
(4) Y^J is not a single bond, when A^J is (ii) -O-R^{0J} or -S(O)p^J-R^{0J} or (iii) - $NR^{16J}R^{17J}$;

or pharmaceutically acceptable acid addition salts thereof, pharmaceutically acceptable salts thereof, or hydrates thereof.

Thienopyrimidine derivatives useful as plant protection agents against fungi, viruses, bacteria and insects have been published (see USP-4146716). In this specification, the thienopyrimidine derivatives of the following formula are disclosed.



(K)

wherein R^{1k} and R^{3k} are H, NH_2, alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl or acyl, optionally substituted ; -$NR^{1k}R^{3k}$ forms a heterocyclic ring; R^{2k} is H halogen atom, OH, SH, CN, NH_2, -$NHNH_2$, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, alkylthio optionally substituted by alkanesuphonyl or alkanesulphinyl, carboxylic acid, ester or amide group or heterocyclic group; R^{5k} and R^{6k} are H, halogen atom, NO_2, halosulphonyl, CN, alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, acyl, alkylamino, aroyl, NH_2, acyloxy, amidosulphonyl, alkylthio, optionally substituted by alkanesuphonyl, carboxylic acid, ester or amide group or R^{5k} and R^{6k} together form a ring.

Thiopyranopyrimidine derivatives having hypoglycaemic activity have been published (see Chem. Pharm. Bull., **34**, 4150 (1986)).

Investigation has been carried out in order to discover compounds having inhibitory activities on cGMP-PDE or additionally TXA_2 synthetase, and as a result, the present inventors have found the compounds of the present invention.

The present invention provides:
heterocyclic compounds of the formula (I):

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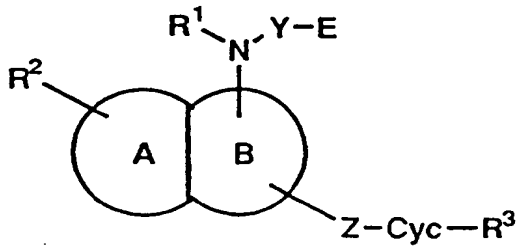
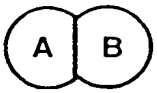
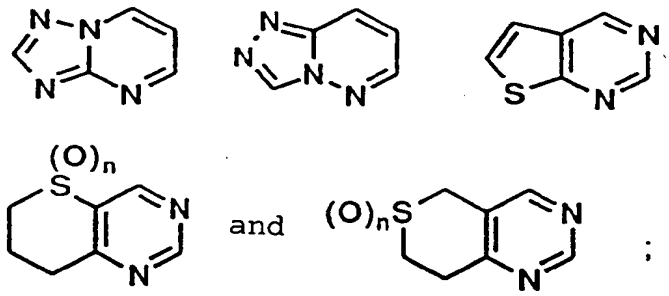


(I)

wherein



is a heterocycle selected from



wherein
n is 0, 1 or 2;
Y is single bond or C1-6 alkylene;
Z is single bond, C1-2 alkylene or vinylene;
E is

(i) 4-15 membered, unsaturated, partially saturated or fully saturated, mono or bicyclic hetero ring containing one or two hetero atoms, chosen from nitrogen, oxygen and sulfur atom, not more than one hetero atom being sulfur,
(ii) 4-15 membered, unsaturated or partially saturated, mono or bicyclic carbocyclic ring, or
(iii) $-OR^4$ (in which R^4 is hydrogen atom, C1-4 alkyl or C1-4 alkyl substituted by a hydroxy group);

Cyc is 5-7 membered, unsaturated, partially saturated or fully saturated, monocyclic hetero ring containing one or two nitrogen atoms
or 5-7 membered, unsaturated or partially saturated, monocyclic carbocyclic ring;
R^1 is hydrogen atom or C1-4 alkyl;
R^2 is hydrogen atom, C1-4 alkyl, C1-4 alkoxy or halogen atom;
R^3 is hydrogen atom, C1-4 alkyl, C1-4 alkoxy or $-COOR^5$ (in which R^5 is hydrogen atom or C1-4 alkyl);
with the proviso that

(1) a Cyc ring does not bond to Z through a nitrogen atom in the Cyc ring when Z is vinylene and that
(2) Y is not a single bond, when E is $-OR^4$;

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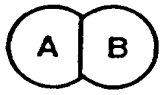
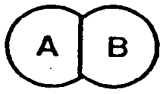
and pharmaceutically acceptable acid addition salts, pharmaceutically acceptable salts and hydrates thereof.

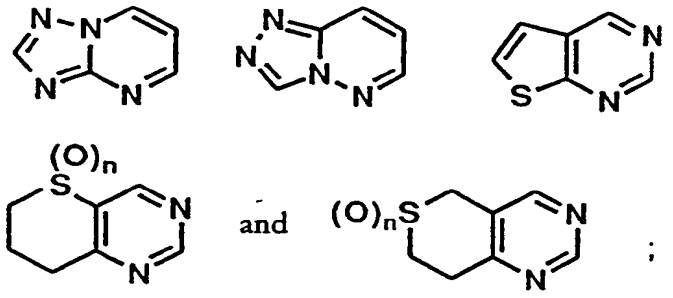
There is no description of the compounds of the formula (I) of the present invention in those of the formulae (E), (F) and (J) mentioned above. The compounds of the formula (I) of the present invention have the following ring of the formula:



(wherein



is a hetero ring containing nitrogen atom, selected from



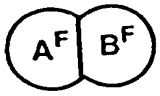
;

) in their structure.

On the other hand, the basic skeleton of the compounds of the formula (E) is a ring system of the formula:

(wherein ring A^E is benzene, pyridine or cyclohexane ring; ring B^E is pyridine, pyrimidine or imidazole ring).

The basic skeleton of the compounds of formula (F) is a ring system of the formula:



(wherein ring A^F is benzene, pyridine or cyclohexane ring; ring B^F is pyridine, pyrimidine or imidazole ring).

Further, the compounds of formula (J) merely have a quinazoline basic skeleton.

BNSDOCID: <EP___0728759A1_I_>

The ring structure of the compounds in the related arts differ from those of the compounds of the present invention e.g. in the types of rings, number of hetero atoms contained in the rings and/or number of rings.

Accordingly, the compounds of the present invention are novel. Furthermore, the fact that compounds of the present invention have inhibitory activity on cGMP-PDE or additionally TXA_2 synthetase, is not suggested from pharmaceutical use disclosed in related arts of (E) and (F) mentioned above.

The compounds of the present invention are useful for the prevention and/or treatment of diseases induced by enhancement of the metabolism of cGMP or by an increase in TXA_2, or induced by both factors.

In the formula (I), the C1-4 alkyl group represented by R^1, R^2, R^3, R^4 in E and R^5 means methyl, ethyl, propyl, butyl and the isomers thereof.

In the formula (I), the C1-4 alkoxy group represented by R^2 and R^3 means methoxy, ethoxy, propoxy, butoxy and isomers thereof.

In the formula (I), the halogen atom represented by R^2 means fluorine, chlorine, bromine and iodine.

In the formula (I), the C1-6 alkylene group represented by Y means methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene and isomers thereof.

In the formula (I), the C1-2 alkylene group represented by Z means methylene, ethylene and isomers thereof.

In the formula (I), the C1-4 alkyl substituted by a hydroxy group represented by R^4 in F means methyl, ethyl, propyl, butyl and the isomers thereof, which are substituted by a hydroxy group.

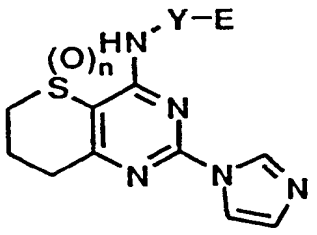
In the formula (I), 5-7 membered, unsaturated, partially saturated or fully saturated, monocyclic hetero ring containing one or two nitrogen atoms represented by Cyc includes pyrrole, pyrroline, pyrrolidine, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, pyridine, piperidine, pyridazine, pyrimidine, pyrazine, piperazine and azepine.

In the formula (I), 5-7 membered, unsaturated or partially saturated, monocyclic carbocyclic ring represented by Cyc includes cyclopentadiene, cyclopentene, benzene, cyclohexadiene, cyclohexene, cycloheptatriene, cycloheptadiene and cycloheptene.

In the formula (I), 4-15 membered, unsaturated, partially saturated or fully saturated, mono or bicyclic hetero ring containing one or two hetero atoms, chosen from nitrogen, oxygen and sulfur, not more than one hetero atom being sulfur, represented by E includes furan, pyran, dioxole, dioxine, benzofuran, benzopyran, benzodioxole, benzodioxine, thiophene, thioine (thiopyran), benzothiophene, benzothione (benzothiopyran), thiazole, isothiazole, thiazine, benzothiazole, benzoisothiazole, benzothiazine and partially or fully saturated analogues thereof.

In the formula (I), 4-15 membered, unsaturated or partially saturated, mono or bicyclic carbocyclic ring represented by E includes cyclopentadiene, benzene, cycloheptatriene, indene, naphthalene and partially saturated analogues thereof.

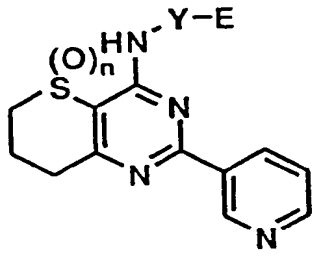
In the compounds of formula (I), Y is preferably single bond, methylene or ethylene. Z is preferably single bond. E is preferably pyridinyl, benzodioxanyl, phenyl, methoxy or hydroxyethoxy. Cyc is preferably imidazolyl, piperidinyl or phenyl; R^1 is preferably hydrogen. R^2 is preferably hydrogen or methyl. R^3 is preferably carboxy or ethoxycarbonyl. Preferred compounds of the present invention are listed as follows: heterocyclic compounds of the formula (IA)



(IA)

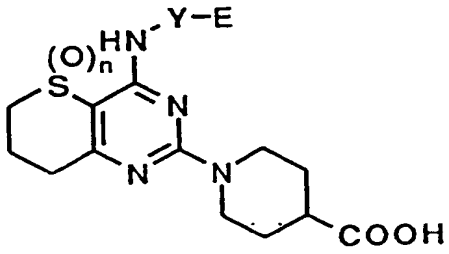
BNSDOCID: <EP___0728759A1_I_>

wherein Y, E and n are as hereinbefore defined, the formula (IB)



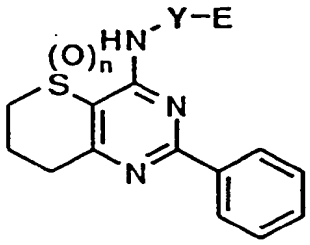
(IB)

wherein Y, E and n are as hereinbefore defined, the formula (IC)



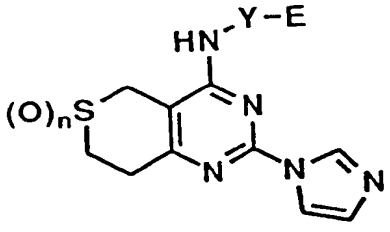
(IC)

wherein Y, E and n are as hereinbefore defined, the formula (ID)



(ID)

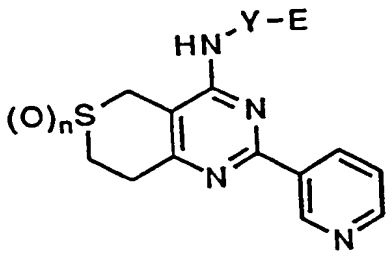
wherein Y, E and n are as hereinbefore defined, the formula (IE)



(IE)

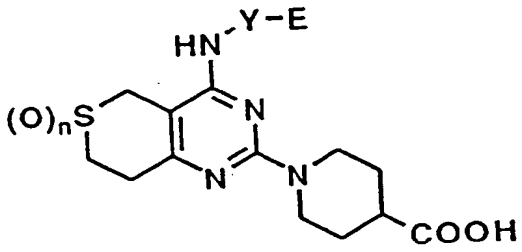
BNSDOCID: <EP___0728759A1_|_>

wherein Y, E and n are as hereinbefore defined, the formula (IF)



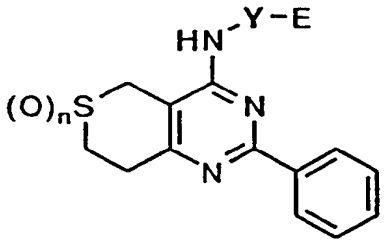
(IF)

wherein Y, E and n are as hereinbefore defined, the formula (IG)



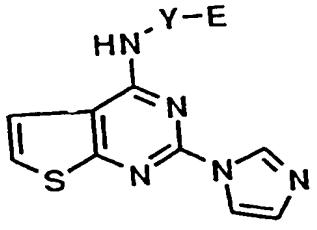
(IG)

wherein Y, E and n are as hereinbefore defined, the formula (IH)



(IH)

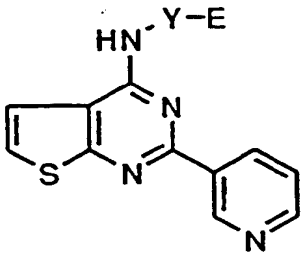
wherein Y, E and n are as hereinbefore defined, the formula (IJ)



(IJ)

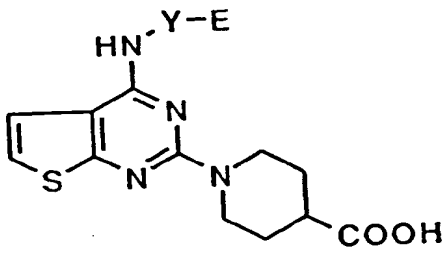
BNSDOCID: <EP___0728759A1_I_>

wherein Y, E and n are as hereinbefore defined, the formula (IK)



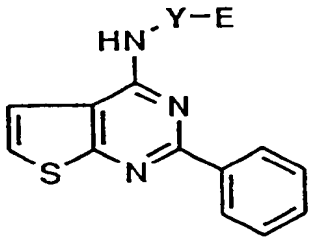
(IK)

wherein Y, E and n are as hereinbefore defined, the formula (IL)



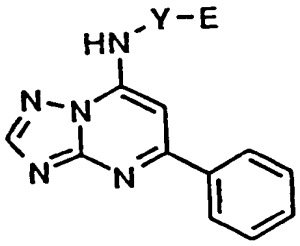
(IL)

wherein Y, E and n are as hereinbefore defined, the formula (IM)



(IM)

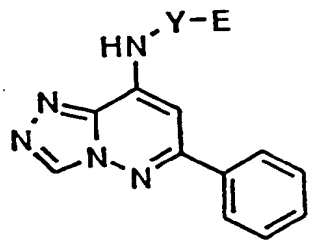
wherein Y, E and n are as hereinbefore defined, the formula (IN)



(IN)

BNSDOCID: <EP___0728759A1_I_>

wherein Y, E and n are as hereinbefore defined, the formula (IO)



(IO)

wherein Y, E and n are as hereinbefore defined, pharmaceutically acceptable acid addition salts thereof, pharmaceutically acceptable salts thereof and hydrates thereof.

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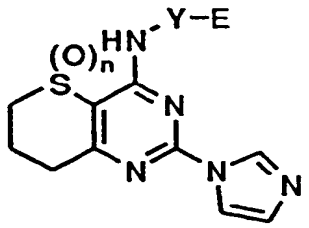
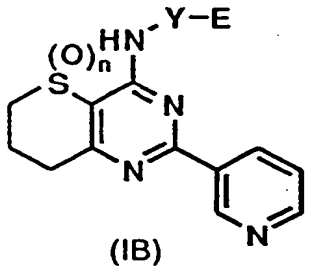
Examples of representative compounds of the present invention are listed as follows:

Table 1



(IA)



(IB)

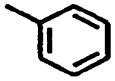
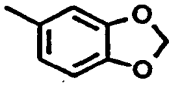
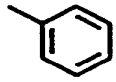
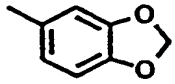
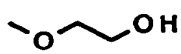
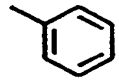
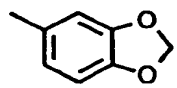
No.		n	Y	E
1	(IA) or (IB)	0	methylene	
2	(IA) or (IB)	0	methylene	
3	(IA) or (IB)	0	ethylene	
4	(IA) or (IB)	1	methylene	
5	(IA) or (IB)	1	methylene	
6	(IA) or (IB)	1	ethylene	
7	(IA) or (IB)	2	methylene	
8	(IA) or (IB)	2	methylene	
9	(IA) or (IB)	2	ethylene	

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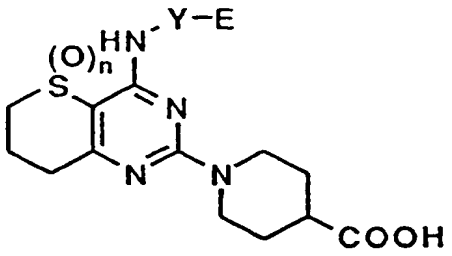
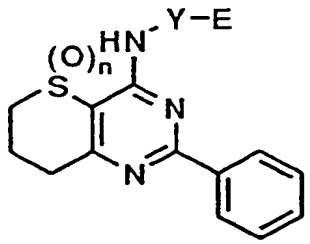
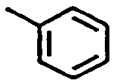
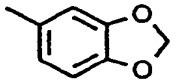
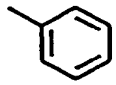
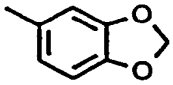
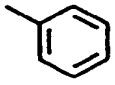
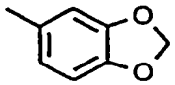
Table 2



(IC)

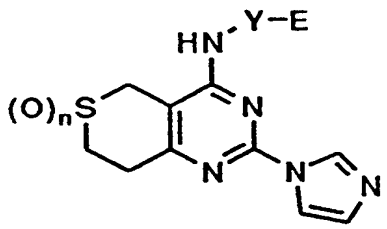


(ID)

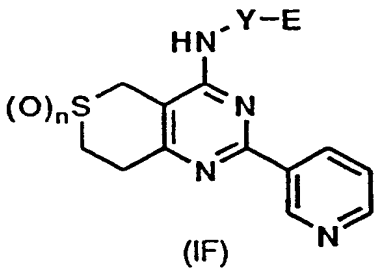
No.		n	Y	E
1	(IC) or (ID)	0	methylene	
2	(IC) or (ID)	0	methylene	
3	(IC) or (ID)	0	ethylene	
4	(IC) or (ID)	1	methylene	
5	(IC) or (ID)	1	methylene	
6	(IC) or (ID)	1	ethylene	
7	(IC) or (ID)	2	methylene	
8	(IC) or (ID)	2	methylene	
9	(IC) or (ID)	2	ethylene	

BNSDOCID: <EP___0728759A1_I_>

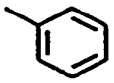
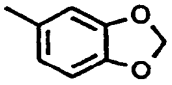
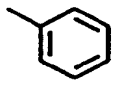
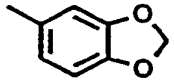
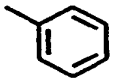
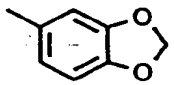
Table 3



(IE)

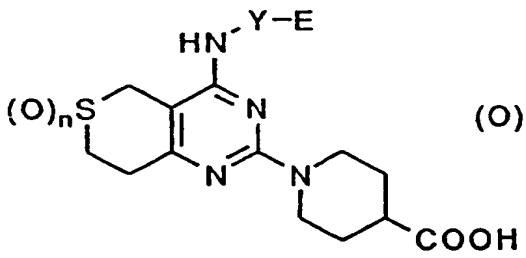


(IF)

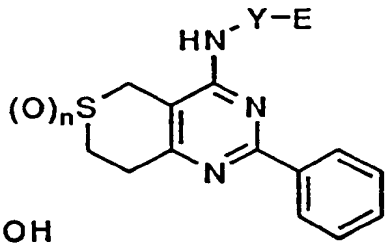
No.		n	Y	E
1	(IE) or (IF)	0	methylene	
2	(IE) or (IF)	0	methylene	
3	(IE) or (IF)	0	ethylene	
4	(IE) or (IF)	1	methylene	
5	(IE) or (IF)	1	methylene	
6	(IE) or (IF)	1	ethylene	
7	(IE) or (IF)	2	methylene	
8	(IE) or (IF)	2	methylene	
9	(IE) or (IF)	2	ethylene	

BNSDOCID: <EP___0728759A1_I_>

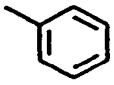
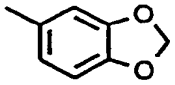
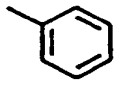
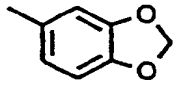
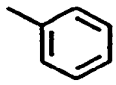
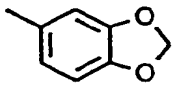
Table 4



(IG)

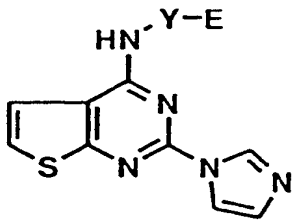


(IH)

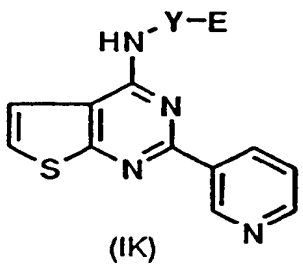
No.		n	Y	E
1	(IG) or (IH)	0	methylene	
2	(IG) or (IH)	0	methylene	
3	(IG) or (IH)	0	ethylene	
4	(IG) or (IH)	1	methylene	
5	(IG) or (IH)	1	methylene	
6	(IG) or (IH)	1	ethylene	
7	(IG) or (IH)	2	methylene	
8	(IG) or (IH)	2	methylene	
9	(IG) or (IH)	2	ethylene	

BNSDOCID: <EP___0728759A1_I_>

Table 5



(IJ)



(IK)

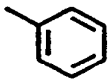
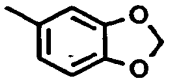
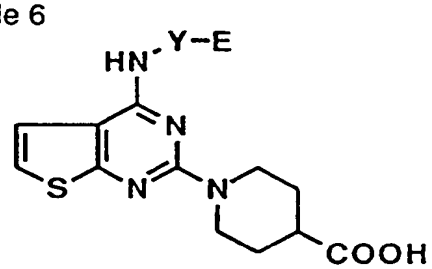
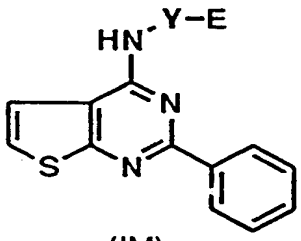
No.		Y	E
1	(IJ) or (IK)	methylene	
2	(IJ) or (IK)	methylene	
3	(IJ) or (IK)	ethylene	

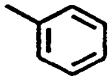
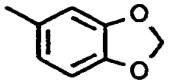
Table 6



(IL)

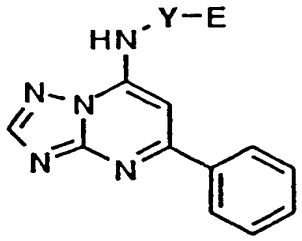


(IM)

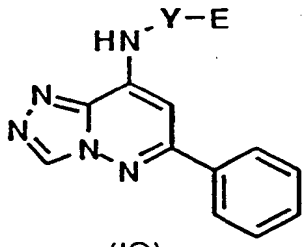
No.		Y	E
1	(IL) or (IM)	methylene	
2	(IL) or (IM)	methylene	
3	(IL) or (IM)	ethylene	

BNSDOCID: <EP___0728759A1_I_>

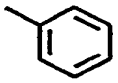
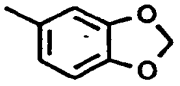
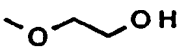
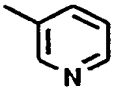
Table 7



(IN)



(IO)

No.		Y	E
1	(IN) or (IO)	methylene	
2	(IN) or (IO)	methylene	
3	(IN) or (IO)	ethylene	
4	(IN) or (IO)	methylene	

and further those described in Examples below are also representative compounds of the present invention.

The compounds of the formula (I), if desired, may be converted into acid addition salts by known methods. Preferably, such acid addition salts are non-toxic and water-soluble. The suitable acid addition salts are, for example, salts of an inorganic acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, nitric acid, or an organic acid such as acetic acid, lactic acid, tartaric acid, benzoic acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, isethionic acid, glucuronic acid and gluconic acid.

The compounds of the formula (I), if desired, may be converted into salts by known methods. Preferably such salts are non-toxic and water-soluble. Suitable salts include salts of alkali metals (e.g. sodium or potassium), salts of alkaline earth metals e.g. calcium or magnesium), ammonium salts, salts of pharmaceutically acceptable organic amines (e.g. tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, phenylmethylamine, phenethylamine, piperidine, monoethanolamine diethanolamine, tris(hydroxymethyl)methylamine, lysine, arginine or N-methyl-D-glucamine).

Throughout the specification including claims, it may be easily understood by those skilled in the art, that the alkyl, alkoxy and alkylene groups may be straight-chained or branched-chained. Accordingly, all isomers produced by the difference in stereo configuration, such as asymmetric carbons, are included in the present invention

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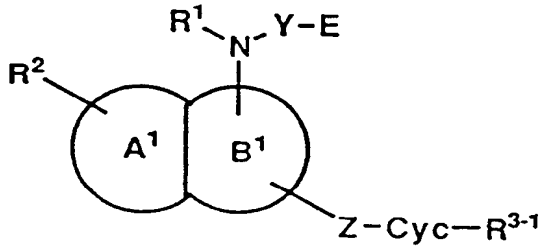
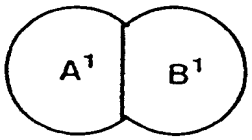
The compounds of formula (I) of the present invention which are of formula (I-1)

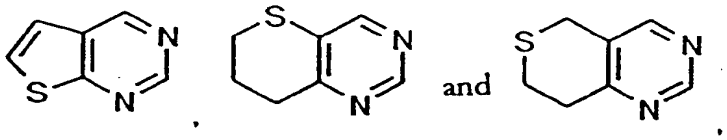


(I-1)

wherein

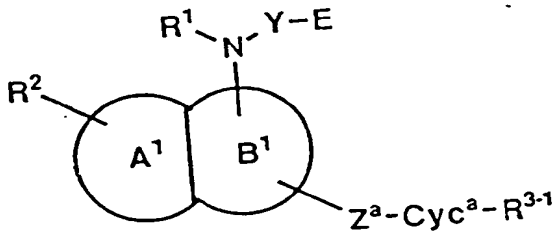


is selected from



R^{3-1} is as hereinbefore defined for R^3 except that R^{3-1} does not represent a COOH group, and the other symbols are as hereinbefore defined
may be prepared by the following methods (a) to (c).

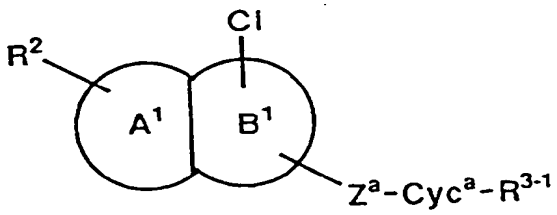
(a) Compounds of formula (I-1) in which Z is as hereinbefore defined and Z is bonded directly to a carbon atom in the ring represented by Cyc, i.e., compounds of the formula (I-a)



(I-a)

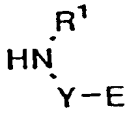
wherein Z^a is as hereinbefore defined for Z and Cyc^a is as hereinbefore defined for Cyc, provided that Z^a is bonded directly to a carbon atom in the ring represented by Cyc^a, and the other symbols are as hereinbefore defined, may be prepared by reacting a compound of the formula (II-a)

BNSDOCID: <EP___0728759A1_I_>



(II-a)

wherein all symbols are as hereinbefore defined with an amine of the formula (III)

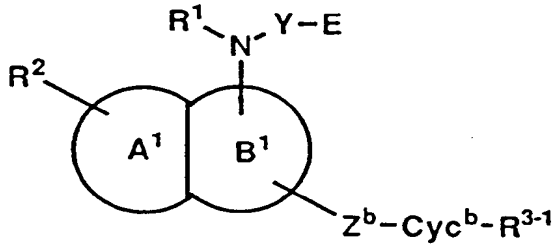


(III)

wherein all symbols are as hereinbefore defined.

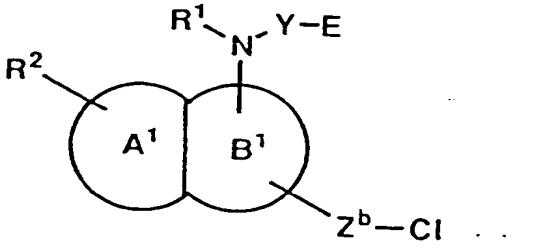
This reaction may be carried out, for example, in a suitable organic solvent such as a lower alkanol (e.g. ethanol) or tetrahydrofuran, or a mixture thereof, at a temperature from ambient to reflux, for several hours to several days, if necessary in the presence of a base such as triethylamine.

(b) Compounds of formula (I-1) in which Z represents single bond or methylene and Z is bonded directly to a nitrogen atom in the hetero ring represented by Cyc, i.e., compounds of the formula (I-b)



(I-b)

wherein Z^b is single bond or methylene and Cyc^b is as hereinbefore defined for Cyc, provided that Z^b is bonded directly to a nitrogen atom in the ring represented by Cyc^b, and the other symbols are as hereinbefore defined, may be prepared by reacting a compound of the formula (II-b)



(II-b)

wherein all symbols are as hereinbefore defined with a heterocyclic amine of the formula (IV)

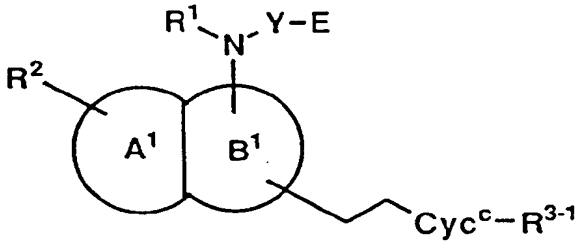
$$H—Cyc^b\text{-}R^{3\text{-}1} \qquad \text{(IV)}$$

wherein all symbols are as hereinbefore defined.

BNSDOCID: <EP___0728759A1_I_>

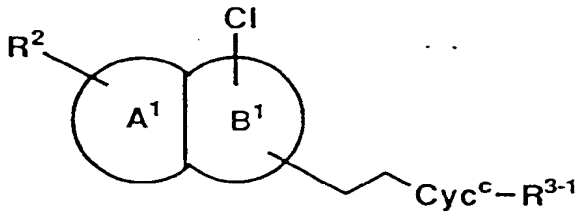
This reaction may be carried out, for example, in a suitable organic solvent such as an alcohol (e.g. phenol or isopropyl alcohol) at a reflux temperature for several hours.

(c) Compounds of formula (I-1) in which Z represents ethylene and Z is bonded directly to a nitrogen atom in the hetero ring represented by Cyc, i.e., compounds of the formula (I-c)



(I-c)

wherein Cyc^c is as hereinbefore defined for Cyc, provided that ethylene is bonded directly to a nitrogen atom in the ring represented by Cyc^c, and the other symbols are as hereinbefore defined, may be prepared by reacting a compound of the formula (II-c)

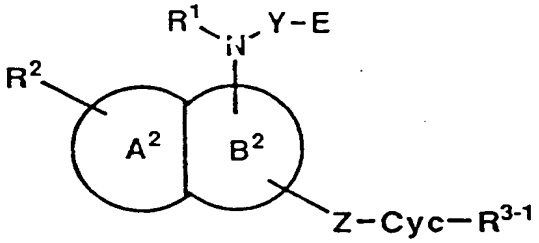


(II-c)

wherein all symbols are as hereinbefore defined with an amine of the formula (III).

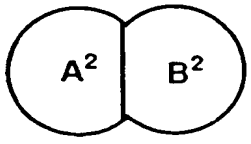
This reaction may be carried out by the same method as hereinbefore described for compounds of formula (I-a).

The compounds of formula (I) of the present invention which are of formula (I-2)



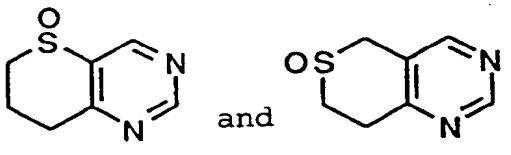
(I-2)

wherein

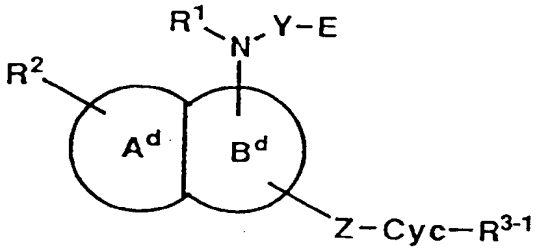


BNSDOCID: <EP___0728759A1_I_>

is selected from

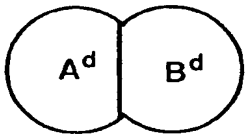


and the other symbols are as hereinbefore defined, may be prepared by oxidation of a corresponding compound having a sulfide group, prepared, for example, by a method as hereinbefore described, i.e., of a compound of the formula (I-d)

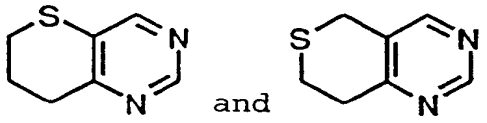


(I-d)

wherein



is selected from

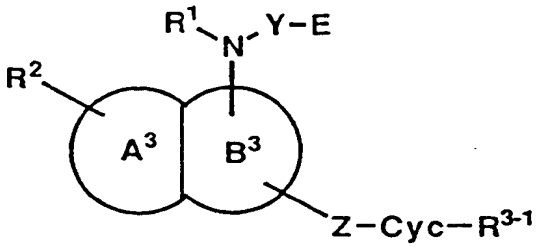


and the other symbols are as hereinbefore defined.

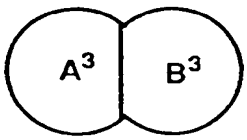
The reaction may be carried out, for example, in a suitable organic solvent (e.g., dichloromethane, chloroform, benzene, hexane or t-butyl alcohol) in the presence of 1 equivalent of oxidation reagent (e.g., hydrogen peroxide, sodium periodate, acyl nitrites, sodium perborate or peracid (for example 3-chloroperoxybenzoic acid, peracetic acid)), at a temperature from -40 °C to 0 °C for several minutes.

BNSDOCID: <EP___0728759A1_I_>

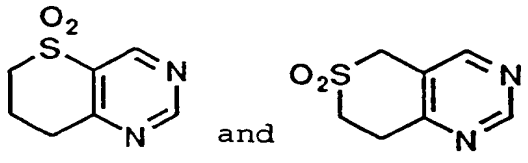
The compounds of formula (I) of the present invention which are of formula (I-3)



(I-3)



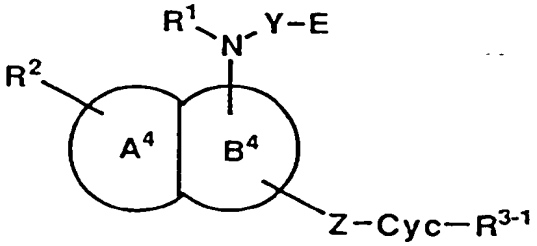
wherein is selected from



and the other symbols are as hereinbefore defined, may be prepared by oxidation of a corresponding compound having a sulfide group of the formula (I-d), or by oxidation of a corresponding compound having a sulfinyl group of the formula (I-2).

This reaction may be carried out, for example, in a suitable organic solvent (e.g., dichloromethane, chloroform, benzene, hexane or t-butyl alcohol) in the presence of excess of oxidation reagent (e.g., hydrogen peroxide, sodium periodate, potassium permanganate, sodium perborate, potassium hydrogen persulfate or peracid (for example 3-chloroperoxybenzoic acid, peracetic acid)), at a temperature from 0 °C to 40 °C for several hours.

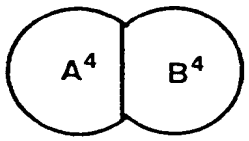
The compounds of formula (I) of the present invention which are of formula (I-4)



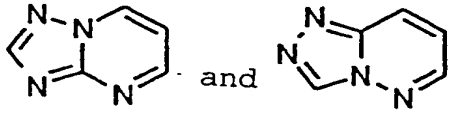
(I-4)

BNSDOCID: <EP___0728759A1_I_>

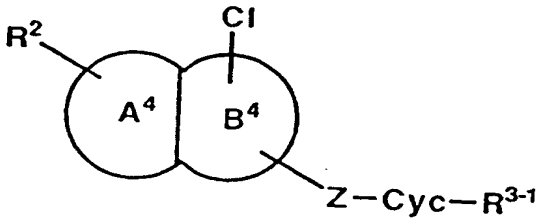
wherein



is selected from



and the other symbols are as hereinbefore defined, may be prepared by reacting a compound of the formula (II-d)

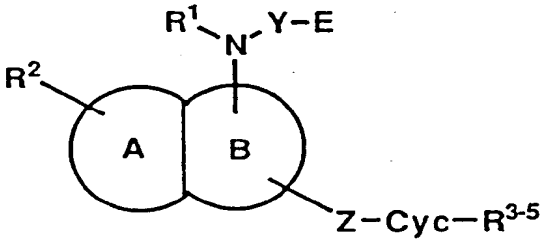


(II-d)

wherein all symbols are as hereinbefore defined, with an amine of the formula (III).

This reaction may be carried out by the same method as hereinbefore described for compounds of formula (I-a).

The compounds of formula (I) of the present invention which are of formula (I-5)



(I-5)

wherein R^{3-5} represents a COOH group, and the other symbols are as hereinbefore defined, may be prepared by hydrolysis of a compound of the formula (I-1), (I-2), (I-3) or (I-4) having an ester group, i.e., a compound of the formula (I-f)

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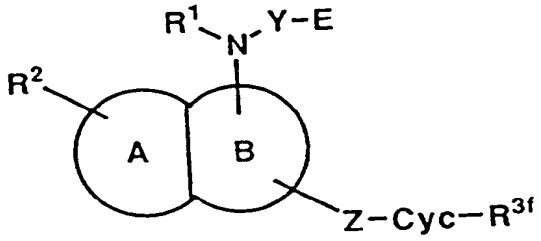

(I-f)

wherein R^{3f} represents $COOR^{5f}$ (in which R^{5f} represents C1-4 alkyl), and the other symbols are as hereinbefore defined.

Hydrolysis of an ester bond is known *per se*, for example, under alkaline or acid conditions. Hydrolysis in alkaline conditions may be carried out, for example, in an appropriate organic solvent (e.g., methanol), using a hydroxide or a carbonate of an alkali metal or alkaline earth metal, at a temperature of from 0 °C to 40 °C. Hydrolysis in acid conditions may be carried out, for example, in an appropriate organic solvent (e.g., dichloromethane, chloroform, methanol, dioxane, ethyl acetate, anisole), or a mixture of them, in presence of an organic acid (e.g., trifluoroacetic acid), or inorganic acid (e.g., hydrochloric acid, sulfuric acid), or a mixture of them, at a temperature of from 0 °C to 90 °C.

The compounds of the formulae (II-a), (II-b), (II-c) or (II-d) may be prepared by using known reactions. For example, they may be prepared by application or adaptation of the methods of Schemes 1 to 4 or methods described in the Examples.

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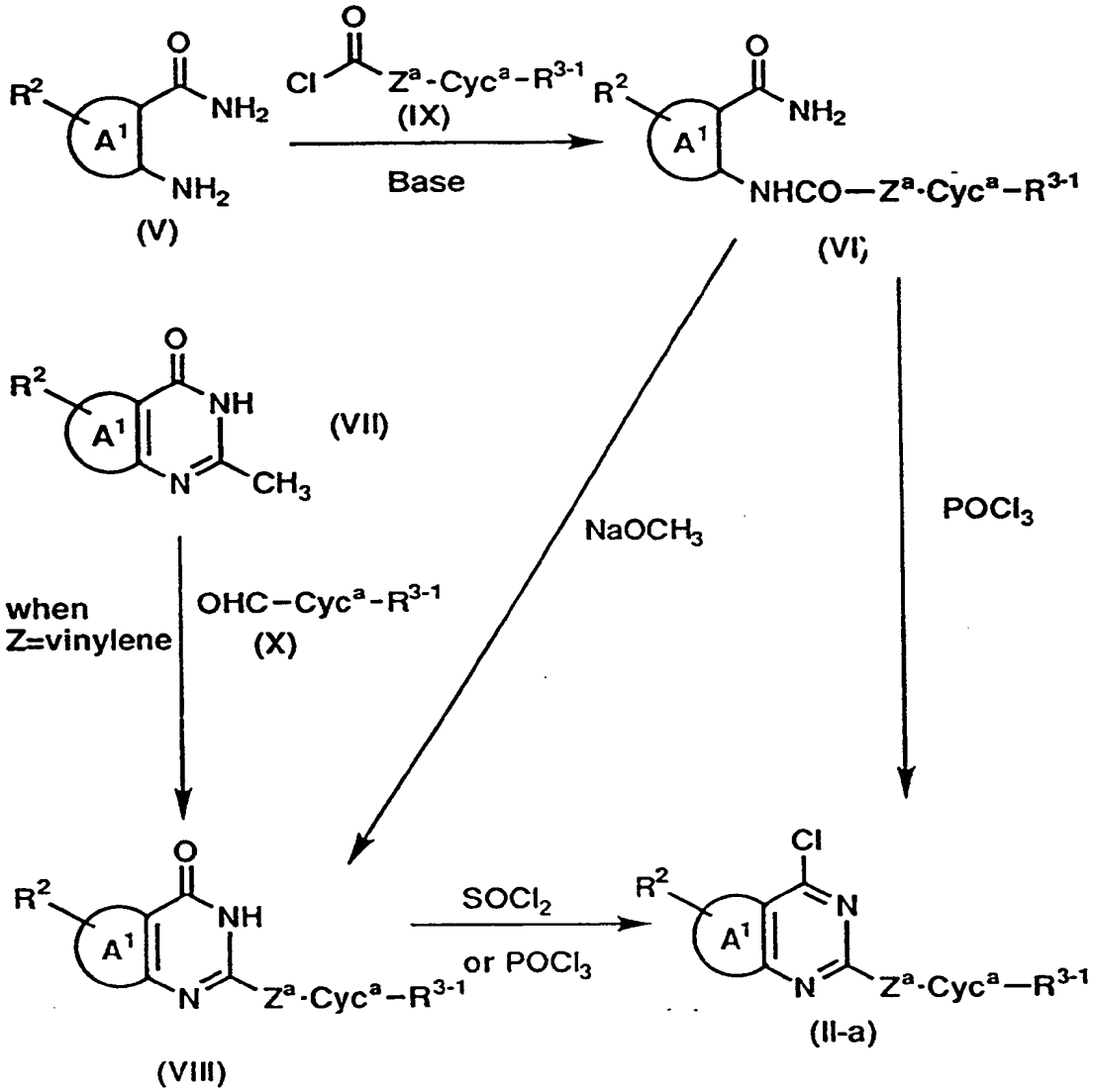
Scheme 1



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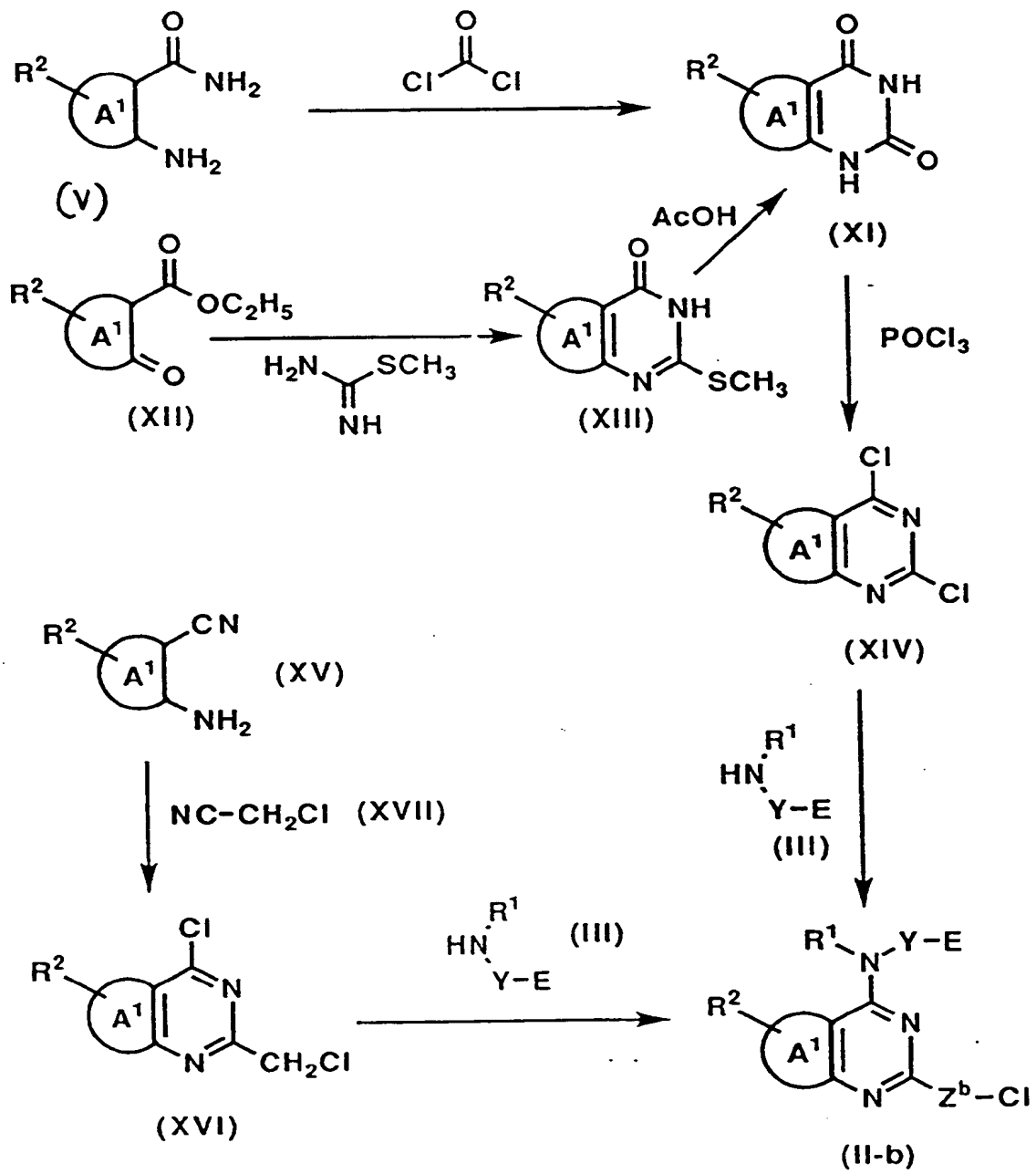
Scheme 2



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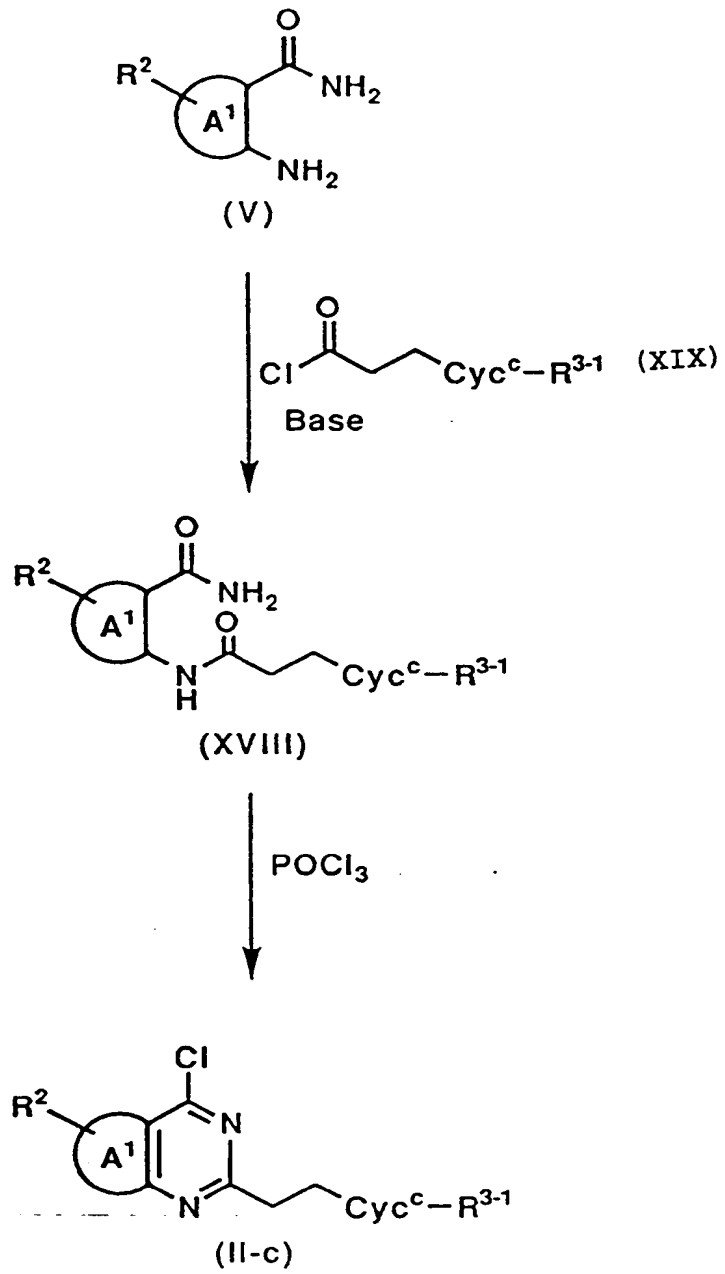
Scheme 3



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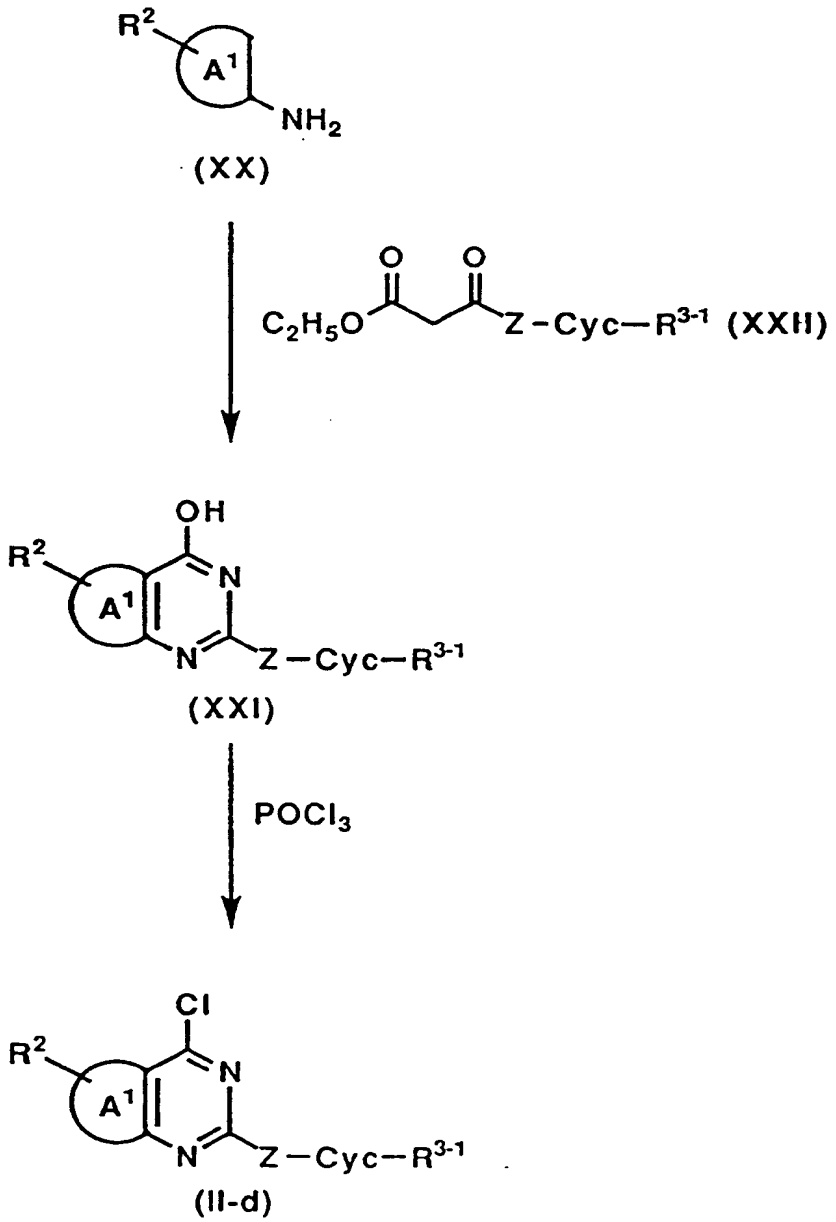
Scheme 4



Each reaction in Scheme 1 to 4 may be carried out by methods known *per se*, under conditions described therein.

In each reaction in the present specifcation, products may be purified by conventional manner. For example, it may be carried out by distillation at atmospheric or reduced pressure, high performance liquid chromatography, thin layer chromatography or column chromatography using silica gel or magnesium silicate, washing or recrystallization. Purification may be carried out after each reaction, or after a series of reactions.

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The starting materials and each reagent used in the preparation processes of the present invention are known *per se* or may be easily prepared by known methods.

The compounds of the formula (I), pharmaceutically acceptable acid addition salts thereof, pharmaceutically acceptable salts thereof, or hydrates thereof, of the present invention have an inhibitory effect on cGMP-PDE, or additionally on TXA_2 synthetase, and are, therefore, useful for the prevention and/or treatment of not only diseases induced by enhancement of the metabolism of cGMP, such as hypertension, heart failure, myocardial infarction, angina, atherosclerosis, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, asthma, bronchitis, dementia, immunodeficiency, pulmonary hypertension, but also diseases induced by enhancement of the synthesis of TXA_2 such as inflammation, thrombosis, cerebral apoplexy, asthma, cardiostenosis or cerebral infarction, in mammals, especially in humans.

The inhibitory effect on cGMP-PDE and TXA_2 synthetase, of the compounds of the present invention were confirmed by screening tests as described below.

(1) Inhibitory effect on cGMP-PDE

Method

PDE IC was isolated from human platelets according to standard methods previously described in Lugnier, C. et al, *Biochem. Pharmacol.* **35**: 1743, 1986 (incorporated in its entirety by reference). Typically, connective tissue and adventitia were removed and 1-2 units of platelets were suspended in 10 volumes of buffer A (20 mM Tris-HCl, pH 7.5, containing 2 mM magnesium acetate, 1 mM dithiothreitol, and 5 mM Na2EDTA) using a Brinkman polytron. The proteinase inhibitors leupeptin, pepstatin A, and phenylmethyl-sulfonyl fluoride (PMSF) were also included in this buffer (final concentration of 100 nM each). The homogenate was centrifuged at 100,000 g for 60 minutes. The supernatant was then removed and filtered through four layers of cheesecloth. The supernatant was applied to a DWAE-Trisacryl M column. The column was washed with several bed volumes of buffer B (20 mM Tris-HCl, pH 7.5, containing 2 mM magnesium acetate, 1 mM dithiothreitol, and proteinase inhibitors) and eluted by two successive linear NaCl gradients (0.05-0.15 M, 300 ml total; 0.15-0.40 M, 200 ml total). Five milliliter fractions were collected and assayed for cyclic GMP PDE activity.

Phosphodiesterase activity was measured, as described by Thompson, et al, *Adv. Cyclic Nucleotide Res.* **10**:69, 1979 (incorporated in its entirety by reference), in a reaction medium containing 40 mM Tris-HCl (pH 8.0), 5 mM $MgCl_2$, and 1 mM dithiothreitol. The concentration of substrate (^{3}H-cGMP) was 0.2 mM. Compounds of the present invention were dissolved in dimethyl sulfoxide (DMSO) at a final concentration of 2.5%. This concentration of DMSO inhibited enzyme activity by approximately 10%. The IC_{50} values (concentration that produced 50% inhibition of substrate hydrolysis) for the compounds examined were determined from concentration-response curves in which concentrations typically ranged from 10^{-8} to 10^{-3} M for the less potent inhibitors (half-log increments).

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Result

Table 8

Inhibitory activity on cGMP-PDE		
Compounds Example No.		Inhibitory activity IC_{50} (M)
2	(2HCl salt)	1.25×10^{-7}
2(3)	(2HCl salt)	1.0×10^{-7}
2(5)	(CH_3SO_3H salt)	1.0×10^{-7}
2(7)	(CH_3SO_3H salt)	2.4×10^{-8}
4	(free base)	3.8×10^{-7}
5	(CH_3SO_3H salt)	3.2×10^{-6}
6(1)	(CH_3SO_3H salt)	3.8×10^{-7}
7	(free base)	3.1×10^{-6}
8	(free base)	9.4×10^{-7}

(2) Inhibitory effect on TXA_2 synthetase

Method

Male Wistar rats were starved overnight. Five hundred microliter of heparinized (10U/mL) whole blood was collected from abdominal aorta using polyethylene syringe (needle: 22 or 26G). The blood freshly drawn from animal was preincubated with 5 µl of test compound at 37 °C. Five minutes later, 2.5 µL of 6 mM of Ca ionophore A23187 (final concentration of 30 µM) was added into tube, and incubation mixture was further incubated for 15 min. The reaction was terminated by centrifugation of tubes at 12,000 rpm for 2 min. TXB_2 content in the supernatant was determined by EIA as follows.

One milliliter of 0.5 M glycine-HCl buffer (pH 3.2) was added to 100 µL of sample. The samples were mixed well and centrifuged at 1,700 G for 10 min at 4 °C. The extracted supernatant was applied to a SEP-PAK (registered Trade Mark) C_{18} cartridge (Waters Assoc.). After washing with 10 mL of distilled water followed by 10 mL each of 15% ethanol and petroleum ether, the sample was eluted with 3 mL of ethyl acetate. The ethyl acetate fraction was evaporated to dryness under gentle N_2 stream and the residue was dissolved in EIA buffer (final volume of 1 mL) following the addition of 300 µL of 0.01M $NaHCO_3$-NaOH buffer (pH 10.0). EIA for TXB_2 was carried out according to a legend attached to the kit (Chyman Chemical Co., Inc.). Overall recovery of TXB_2 in this extraction procedure was 90%. The IC_{50} values (concentration that produced 50% inhibition of TXB_2 synthesis) for the compounds examined were determined from concentration-response curves.

Result

Table 9

Inhibitory activity on TXA_2 synthetase	
Compounds Example No.	Inhibitory activity (%)
2(7) (CH_3SO_3H salt)	63% at 10 µM

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On the other hand, it was confirmed that the acute toxicity of the compounds of the present invention is very weak. Therefore, the compounds of the present invention may be considered to be sufficiently safe and suitable for pharmaceutical use.

The present invention accordingly provides a pharmaceutical composition which comprises, as active ingredient, a compound of formula (I) or a pharmaceutically acceptable acid addition salt, pharmaceutically acceptable salt or hydrate thereof; and a pharmaceutically acceptable carrier.

For the purpose above described, the compounds, of the formula (I), of the present invention, pharmaceutically acceptable acid addition salts thereof, pharmaceutically acceptable salts thereof, and hydrates thereof may be normally administered systemically or partially, usually by oral or parenteral administration.

The doses to be administered are determined depending, for example, upon age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment. In the human adult, the doses per person are generally between 1 mg and 1000 mg, by oral administration, up to several times per day, and between 1 mg and 100 mg, by parenteral administration up to several times per day, or continuous administration between 1 and 24 hours per day intravenously.

As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may be used.

Administration of the compounds of the present invention, may, for example, be as solid compositions, liquid compositions or other compositions for oral administration, as injections, liniments or suppositories for parenteral administration.

Solid compositions for oral administration include compressed tablets, pills, capsules, dispersible powders, and granules. Capsules include hard capsules and soft capsules.

In such compositions, one or more of the active compound(s) is or are, admixed with at least one inert diluent (such as lactose, mannitol, glucose, hydroxypropyl cellulose, micro crystalline cellulose, starch, polyvinylpyrrolidone or magnesium metasilicate aluminate). The compositions may also comprise, as is normal practice, additional substances other than inert diluents: e.g. lubricating agents (such as magnesium stearate), disintegrating agents (such as cellulose calcium glycolate), stabilizing agents (such as lactose, and agents to assist dissolution (such as glutamic acid or aspartic acid).

The tablets or pills may, if desired, be coated with film of gastric or enteric material (such as sugar, gelatin, hydroxypropyl cellulose or hydroxypropylmethyl cellulose phthalate), or be coated with two or more films. And further, coating may include containment within capsules of absorbable materials such as gelatin.

Liquid compositions for oral administration include pharmaceutically-acceptable solutions, emulsions, suspensions, syrups and elixirs.

In such compositions, one or more of the active compound(s) is or are comprised in inert diluent(s) commonly used in the art (eg purified water or ethanol).

Besides inert diluents, such compositions may also comprise adjuvants (such as wetting agents or suspending agents), sweetening agents, flavouring agents, perfuming agents and preserving agents.

Other compositions for oral administration include spray compositions which may be prepared by known methods and which comprise one or more of the active compound(s).

Spray composition may comprise additional substances other than inert diluents: e.g. stabilizing agents (such as sodium sulfite and isotonic buffers (such as sodium chloride, sodium citrate or citric acid).

For preparation of such spray compositions, for example, the method described in the United States Patent No. 2868691 or 3095355 may be used.

Injections for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. In such compositions, one or more of active compound(s) is or are admixed with at least one inert aqueous diluent(s) (eg distilled water for injection, physiological salt solution) or inert non-aqueous diluent(s) (eg propylene glycol, polyethylene glycol, olive oil, ethanol POLYSORBATE80 (registered trade mark).

Injections may comprise additional other than inert diluents: e.g. preserving agents, wetting agents, emulsifying agents, dispersing agents, stabilizing agent (eg lactose), assisting agents such as agents to assist dissolution (eg glutamic acid, aspartic acid).

They may be sterilized for example, by filtration through a bacteria-retaining filter, by incorporation of sterilizing agents in the compositions or by irradiation. They also be manufactured in the form of sterile solid compositions, for example, by freeze- drying, and which can be dissolved in sterile water or some other sterile diluents for injection immediately before use.

Other compositions for parenteral administration include liquids for external use, and endermic liniments (ointment etc.), suppositories and pessaries which comprise one or more of the active compound(s) and may be prepared by known methods.

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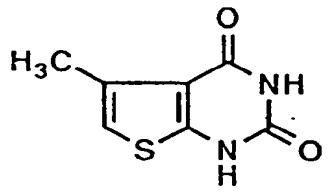
Reference example and Examples

The following Reference examples and examples illustrate the present invention. In Reference examples and examples, "MP" shows "melting point".

Reference example 1

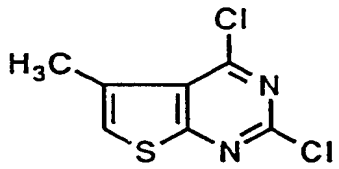


To a solution of 2-amino-4-methylthiophene-3-carboxamide (4.7 g) in 200 mL of tetrahydrofuran was added phosgene (25 mL, 1.93 M solution of toluene) via an addition funnel. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated to a total volume about 10 mL. After cooling, the precipitate was collected by filtration and dried in vacuum to give the title compound (5.3 g) having the following physical data.

MP : 291-292 °C;

NMR (200MHz, DMSO-d6): δ 2.34 (s, 1H), 6.67 (s, 1H), 11.03 (br, 1H), 11.85 (br, 1H).

Reference example 2



To a warmed suspension of the compound prepared in Reference example 1 (1.82 g) in 7 mL of phosphorus oxychloride was added N,N-dimethylaniline (1.21 g). The reaction mixture was heated to reflux for 1.5 hours. After cooling down to room temperature, the reaction mixture was diluted with 30 mL of dichloromethane and then poured into 100 mL of ice-water. The mixture was extracted with dichloromethane (50 mL X 4). The combined extracts were dried over anhydrous sodium sulfate and concentrated to give the title compound (2 g) having the following physical data.

NMR (200MHz, $CDCl_3$): δ 2.68 (m, 3H), 7.22 (m, 1H).

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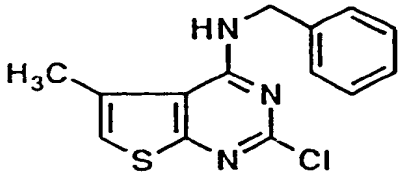
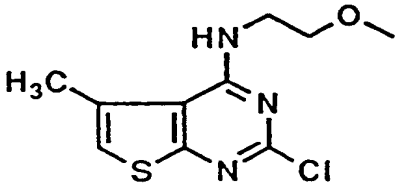
Reference example 3



To a solution of the compound prepared in Reference example 2 (1.1 g) in 40 mL of ethanol was added benzylamine (0.54 g). The mixture was heated to reflux overnight. 0.25 g of triethylamine was added after 1 day and 5 mL of 1N aqueous solution of sodium hydroxide was added after 2 days to above reaction mixture. The mixture was stirred for another 15 minutes. The reaction mixture was concentrated and extracted with dichloromethane (20 mL x3), and dried over potassium carbonate. Removal of solvents under reduced pressure, the residue was triturated in ether and filtered to give the title compound (0.56 g) having the following physical data.

NMR (200MHz, $CDCl_3$): δ 4.84 (d, 2H), 5.81 (br, 1H), 6.85 (m, 1H), 7.35-7.42 (m, 5H).

Reference example 4



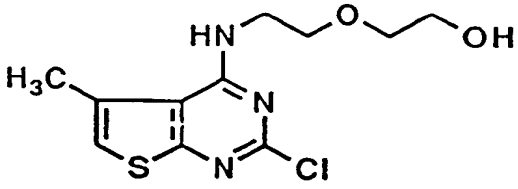
The title compound was obtained by the same procedure as Reference example 3, by using 2-methoxyethylamine instead of benzylamine.

MP : 112-113 °C;

NMR (200MHz, CDCl3): δ 2.57 (s, 3H), 3.43 (s, 3H), 3.62 (t, 2H), 3.80 (t, 2H), 6.08 (brs, 1H), 6.82 (s, 1H);

IR (KBr): ν 3410, 2938, 1578, 1548, 1352, 1249, 979, 893, 740 cm^{-1}.

Reference example 5



The title compound was obtained by the same procedure as Reference example 3, by using 2-(2-hydroxyethoxy)ethylamine instead of benzylamine.

MP : 101-103 °C;

NMR (200MHz, DMSO-d6): δ 2.55 (d, 3H), 3.50 (s, 4H), 3.64 (s, 4H), 4.61 (brs, 1H), 7.01 (brs, 1H), 7.19 (d, 1H);

IR (KBr): ν 3435, 2925, 1582, 1458, 1353, 1132, 1023, 852, 763 cm^{-1}.

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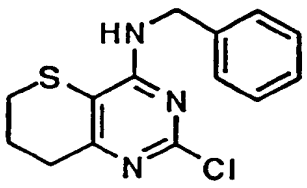
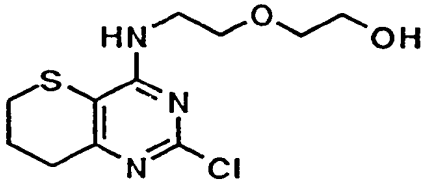
Reference example 6



The title compound was obtained by the same procedure as Reference example 3, by using 2,4-dichloro-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidine (see S. Ohno, et. al, Chem. Pharm. Bull., **34**, 4150 (1986)) instead of the compound prepared in Reference example 2.

TLC: Rf 0.40 (Dichloromethane:Methanol=99:1).

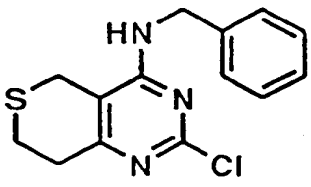
Reference example 7



The title compound was obtained by the same procedure as Reference example 5, by using 2,4-dichloro-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidine instead of the compound prepared in Reference example 2.

TLC: Rf 0.43 (Chloroform:Methanol=19:1).

Reference example 8



The title compound was obtained by the same procedure as Reference example 3, by using 2,4-dichloro-7,8-dihydro-5H-thiopyrano[3,2-d]pyrimidine (the compound prepared by the same procedure as Chem. Pharm. Bull., **34**, 4150 (1986)) instead of the compound prepared in Reference example 2.

TLC: Rf 0.32 (Hexane:Ethyl acetate=3:1);

NMR (200MHz, $CDCl_3$): δ 7.45-7.28 (5H, m), 5.00-4.85 (1H, br), 4.69 (2H, d), 3.35 (2H, s), 3.03 (2H, t), 2.86 (2H, t).

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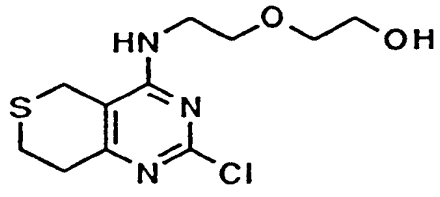
Reference example 9

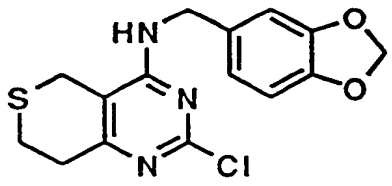


The title compound was obtained by the same procedure as Reference example 5, by using 2,4-dichloro-7,8-dihydro-5H-thiopyrano[3,2-d]pyrimidine instead of the compound prepared in Reference example 2.

TLC: Rf 0.38 (Ethyl acetate);

NMR (200MHz, $CDCl_3$): δ 5.45-5.25 (1H, br), 3.82-3.58 (8H, m), 3.39 (2H, s), 3.02 (2H, t), 2.87 (2H, t), 2.10-1.85 (1H, br).

Reference example 10

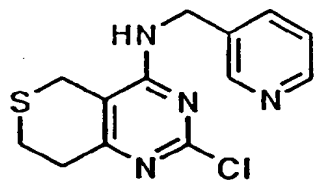


The title compound was obtained by the same procedure as Reference example 8, by using 1,3-benzodioxan-5-methylamine instead of benzylamine.

TLC: Rf 0.19 (Hexane:Ethyl acetate=3:1);

NMR (200MHz, CDCl3): δ 6.85-6.75 (3H, m), 5.96 (2H, s), 4-95-4.80 (1H, br), 4.58 (2H, d), 3.34 (2H, s), 3.02 (2H, t), 2.86 (2H, t).

Reference example 11



The title compound was obtained by the same procedure as Reference example 8, by using 3-(aminomethyl)pyridine instead of benzylamine.

TLC: Rf 0.59 (Chloroform:Methanol=9:1).

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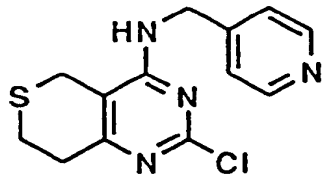
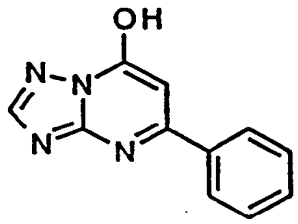
Reference example 12



The title compound was obtained by the same procedure as Reference example 8, by using 4-(aminomethyl)pyridine instead of benzylamine.

TLC: Rf 0.60 (Chloroform:Methanol=9:1).

Reference example 13

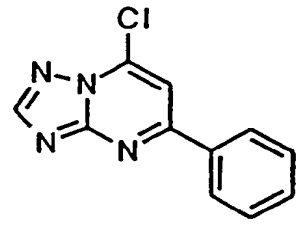


A mixture of 90% ethyl benzoylacetate (22 g) and 3-amino-1,2,4-triazole (8.4 g) in 100 mL of glacial acetic acid was heated at reflux for 18 hours. The mixture was then concentrated to approximately 40 mL and diluted with 400 mL water. The precipitate was collected by filtration. This material was taken up in sodium bicarbonate solution and filtered. The filtrate was acidified with acetic acid and the resulting precipitate was collected by filtration and dried in vacuum to give the title compound (2.3 g) having the following physical data.

MP : 286-288 °C;

NMR (200MHz, DMSO-d6): δ 6.37 (s, 1H), 7.52-7.63 (m, 3H), 7.86-7.97 (m, 2H), 8.41 (s, 1H).

Reference example 14



The title compound was obtained by the same procedure as Reference example 2, by using compound prepared in Reference example 13 instead of the compound prepared in Reference example 1.

MP : 163-170 °C;

NMR (200MHz, $CDCl_3$): δ 7.57 (m, 3H), 7.70 (s, 1H), 8.20 (m, 2H), 8.57 (s, 1H).

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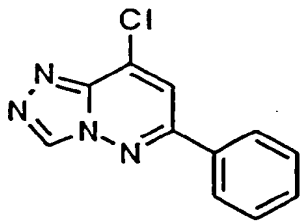
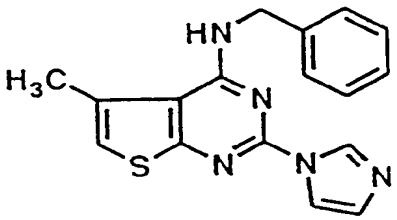
Reference example 15



The title compound was obtained by the same procedure as Reference example 13 and Reference example 14, by using 1-amine-1,2,4-triazole instead of 3-amino-1,2,4-triazole.

NMR (200 MHz, $CDCl_3$): δ 7.56 (m, 3H), 7.67 (s, 1H), 7.97 (m, 2H), 9.19 (s, 1H).

Example 1

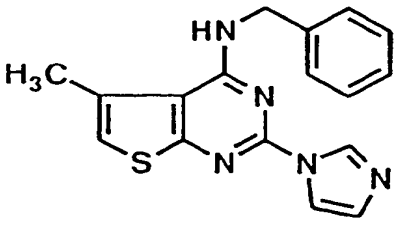


The mixture of the compound prepared in Reference example 3 (0.49 g), imidazole (0.35 g) and phenol (2 g) was heated to reflux for overnight. After cooling down to room temperature, the reaction mixture was diluted with 30 mL of methylene chloride and washed with 1N aqueous solution of sodium hydroxide (10 mL x3) and dried over potassium carbonate. Removal of the solvents by evaporation, the residue was triturated in ether to give the title compound (0.2g) having the following physical data.

MP : 185-189 °C;

NMR (200MHz, $CDCl_3$): δ 2.55 (s, 3H), 4.83 (d, 2H), 5.95 (br, 1H), 6.77 (s, 1H), 7.11 (s, 1H), 7.26-7.40 (m, 5H), 7.86 (s, 1H), 8.55 (s, 1H).

Example 2



· 2HCl

To a suspension of the compound prepared in Example 1 (0.16 g) in 1 mL of methanol was added a saturated methanol solution of hydrochloric acid (0.5 mL) to form a red solution. After stirring at room temperature for 15 minutes, the excess methanol was removed and 10 mL of ether was added to the mixture for triturating. The precipitate was obtained

BNSDOCID: <EP___0728759A1_I_>

after filtration and dried in vacuum to give the title compound (0.17 g) having the following physical data.

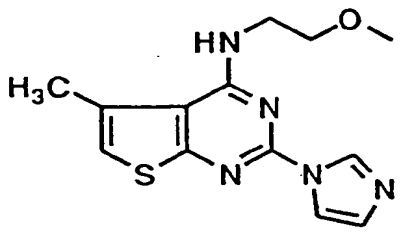
MP : 228-233 °C;

NMR (200MHz, DMSO-d6): δ 2.69 (s, 3H), 4.91 (d, 2H), 7.25-7.40 (m, 4H), 7.49-7.53 (m, 2H), 7.82 (s, 1H), 8.06 (br, 1H), 8.30 (s, 1H), 9.86 (s, 1H).

Example 2(1)-2(7)

The following compounds were obtained by the same procedure as Example 1 and Example 2, by using the corresponding compound prepared by Reference example 4, 5, 6, 7, 8, 9, or 10 and an appropriate amine, if necessary by using the corresponding methanesulfonic acid instead of hydrochloric acid.

Example 2(1)



(• 2HCl)

(free base)

MP : 146-151 °C;

NMR (200MHz, DMSO-d6): δ 2.57 (s, 3H), 3.32 (s, 3H), 3.62 (m, 2H), 3.79 (m, 2H), 7.05 (br, 1H), 7.09 (s, 1H), 7.13 (s, 1H), 7.91 (s, 1H), 8.54 (s, 1H);

IR (KBr): ν 3330, 2925, 1587, 1482, 1423, 1353, 1312, 1099, 1099, 1049, 739, 653 cm^{-1}.

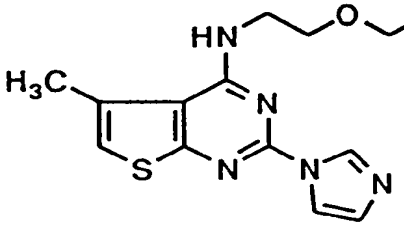
(2HCl salt)

MP : 183-188 °C;

NMR (DMSO-d6): δ 2.61 (s, 3H), 3.32 (s, 3H), 3.62 (t, 2H), 3.85 (q, 2H), 7.29 (s, 1H), 7.33 (brt, 1H), 7.83 (s, 1H), 8.37 (s, 1H), 9.89 (s, 1H);

IR (KBr): ν 3345, 3160, 2800-2500, 1597, 1519, 1403, 1357, 1129, 1050, 832, 768 cm^{-1}.

Example 2(2)



(• 2HCl)

(free base)

MP : 138-140 °C;

NMR (200MHz, DMSO-d6): δ 2.58 (s, 3H), 3.52 (s, 4H), 3.71 (d, 2H), 3.78 (br, 2H), 4.62 (br, 1H), 7.03 (br, 1H), 7.09 (s, 1H), 7.14 (s, 1H), 7.92 (s, 1H), 8.55 (s, 1H);

IR (KBr): ν 3410, 3245, 2920, 1585, 1554, 1475, 1428, 1343, 1312, 1126, 1069, 832 cm^{-1}.

(2HCl salt)

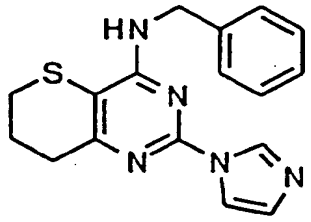
MP : 160-163 °C;

BNSDOCID: <EP___0728759A1_I_>

NMR (200MHz, DMSO-d6): δ 2.62 (s, 3H), 3.52 (s, 4H), 3.71 (t, 2H), 3.85 (t, 2H), 7.30 (s, 2H), 7.82 (s, 1H), 8..38 (s, 1H), 9.87 (s, 1H);

IR (KBr): ν 3435, 3155, 2920, 1601, 1523, 1402, 1129, 1065 cm^{-1}.

Example 2(3)



(• 2HCl)

(free base)

TLC: Rf 0.32 (Dichloromethane:Methanol=19:1);

MP : 165-167 °C;

NMR (200MHz, DMSO-d6): δ 2.12 (m, 2H), 2.76 (m, 2H), 3.12 (m, 2H), 4.65 (d, 2H), 7.01 (s, 1H), 7.20 (t, 1H), 7.30 (t, 2H), 7.39 (d, 2H), 7.59 (m, 1H), 7.72 (s, 1H), 8.33 (s, 1H).

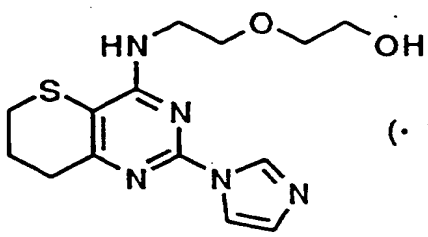
(2HCl salt)

MP : 207.0 - 217.0 °C;

NMR (200 MHz, DMSO-d6): δ 2.03-2.21 (m, 2H), 2.81 (t, 2H), 3.17 (t, 2H), 4.75 (d, 2H), 7.18-7.41 (m, 5H), 7.77 (s, 1H), 7.85 (m, 1H), 8.17 (s, 1H), 9.73 (s, 1H);

IR (KBr): ν 3468, 3274, 1610, 1516, 1428, 1407, 1380, 1053 cm^{-1}.

Example 2(4)



(• 2HCl)

(free base)

TLC: Rf 0.36 (Chloroform:Methanol=19:1);

MASS (EI): 321 (M^+). (2HCl salt)

TLC: Rf 0.36 (Chloroform:Methanol=19:1);

NMR (200MHz, DMSO-d6): δ 9.83 (1H, s), 8.25 (1H, s), 7.82 (1H, s), 7.15 (1H, t), 3.70 (2H, m), 3.61 (2H, t), 3.50-3.40 (4H, m), 3.20-3,10 (2H, m), 2.80 (2H, t), 2.20-2.05 (2H, m);

IR (KBr): ν 3309, 3104, 3013, 2921, 2392, 1884, 1646, 1594, 1577, 1540, 1511, 1389, 1343, 1113, 1061, 1035, 991, 845, 716, 621 cm^{-1}.

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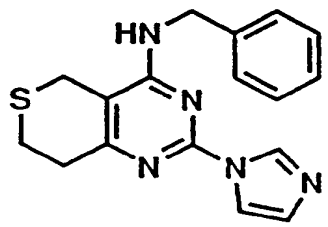
Example 2(5)



• CH_3SO_3H

(free base)

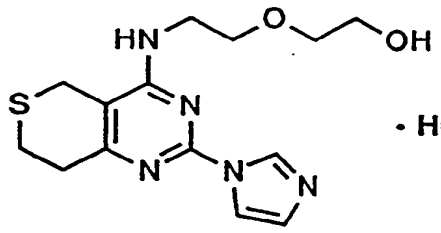
TLC: Rf 0.51 (Ethyl acetate);

NMR (200MHz, DMSO-d6): δ 8.36 (1H, s), 7.95 (1H, t), 7.74 (1H, s), 7.44-7.15 (5H, m), 7.01 (1H, s), 4.66 (2H, d), 3.56 (2H, s), 2.90 (4H s). (CH_3SO_3H salt)

NMR (200MHz, DMSO-d6): δ 9.75 (1H, s), 8.33-8.15 (2H, m), 7.79 (1H, s), 7.48-7.18 (5H, m), 4.75 (2H, d), 3.60 (2H, s), 2.94 (4H, s), 2.34 (3H, s).

IR (KBr): ν 3274, 3140, 1617, 1572, 1543, 1524, 1442, 1413, 1391, 1353, 1212, 1158, 1060, 1046, 895, 836, 772, 704, 625, 555, 527 cm^{-1}.

Example 2(6)



• HCl

(free base)

TLC: Rf 0.56 (Chloroform:Methanol=8:1);

NMR (200MHz, DMSO-d6): δ 8.43 (1H, s), 7.81 (1H s), 7.43-7.25 (1H, br), 7.05 (1H, s), 4.68-4.50 (1H, m), 3.75-3.28 (10H, m), 2.90 (4H, s). (HCl salt)

NMR (200MHz, DMSO-d6): δ 9.78 (1H, s), 8.26 (1H, s), 7.80 (1H, s), 7.77-7.63 (1H, br), 3.78-3.43 (10H, m), 3.08-2.78 (4H, m);

IR (KBr): ν 3401, 2931, 1613, 1523, 1445, 1391, 1350, 1118, 1059, 881, 772, 623 cm^{-1}.

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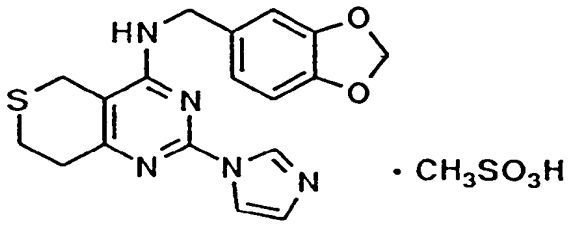
Example 2(7)



(free base)

TLC: Rf 0.33 (Ethyl acetate).

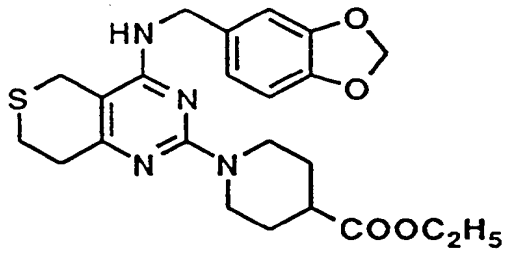
(CH_3SO_3H salt)

TLC: Rf 0.42 (Ethyl acetate);

NMR (200MHz, DMSO-d6): δ 9.76 (1H, s), 8.26 (1H, s), 8.23-8.10 (1H, m), 7.80 (1H, s),7.01 (1H, d), 6.93 (1H, dd), 6.83 (1H, d), 5.95 (2H, s), 4.64 (2H, d), 3.58 (2H, s), 2.94 (4H, s), 2.37 (3H, s);

IR (KBr): ν 3436, 3144, 1616, 1572, 1543, 1524, 1491, 1445,1415, 1393, 1243, 1210, 1159, 1047, 933, 899, 811, 774, 624, 556 cm^{-1}.

Example 3



The mixture of the compound prepared in Reference example 10 (0.333 g), isonipecotic acid ethyl ester (0.95 mL) and isopropyl alcohol (6 mL) was heated to reflux for 1 hour. After cooling down to room temperature, the reaction mixture was diluted with chloroform and washed with water and saturated aqueous solution of ammonium chloride and dried over anhydrous sodium sulfate. Removal of the solvents by evaporation, the residue was purified by silica gel column chromatography (chloroform:ethyl acetate=4:1→2:1) to give the title compound (0.375 g) having the following physical data.

TLC: Rf 0.70 (Chloroform:Ethyl acetate=2:1).

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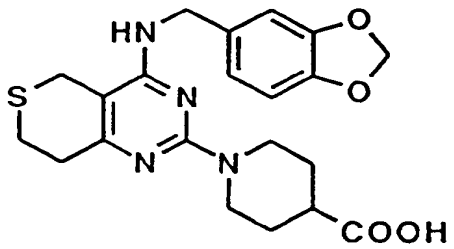
Example (4)



To a solution of the compound prepared in Example 3 (0.375 g) in ethanol (6 mL was added 1N aqueous solution of sodium hydroxide (0.85 mL) at 0 °C. The mixture was stirred at 80 °C for 1.5 hours. The mixture was neutralized by adding 1N aqueous solution of hydrochloric acid and concentrated. The residue was dissolved in methanol and filtered. Removal of the solvents by evaporation to give the title compound (0.259 g) having the following physical data.

TLC: Rf 0.18 (Chloroform:Methanol=6:1);

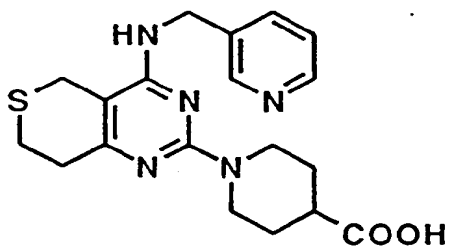
NMR (200MHz, DMSO-d6): δ 7.18 (1H, t), 6.90 (1H, s), 6.82-6.75 (2H, m), 5.94 (2H, s), 4.50-4.31 (4H, m), 3.42 (2H, s), 2.95-2.55 (6H, m), 2.42 (1H, brt) 1.82-1.65 (2H, m), 1.46-1.20 (2H, m);

IR (KBr): ν 3411, 2923, 1655, 1625, 1562, 1489, 1444, 1420, 1369, 1239, 1037, 928, 772 cm^{-1}.

Example 4(1) and 4(2)

The following compounds were obtained by the same procedure as Example 3 and Example 4, by using the corresponding compound prepared by Reference example 11 or 12 instead of the compound prepared in Reference example 10.

Example 4(1)



TLC: Rf 0.17 (Chloroform:Methanol=4:1);

NMR (200MHz, DMSO-d6): δ 8.55 (1H, d), 8.40 (1H, dd), 7.71 (1H, d), 7.30 (1H, dd), 7.26 (1H, brt), 4.51 (2H, d), 4.37 (2H, brd), 3.43 (2H, s), 2.90-2.60 (6H, m), 2.35 (1H, m), 1.80-1.60 (2H, m), 1.42-1.20 (2H, m);

IR (KBr): ν 3399, 2922, 1655, 1626, 1562, 1492, 1420, 1356, 1237, 1032, 714 cm^{-1}.

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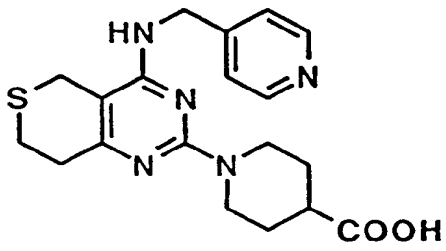
Example 4(2)

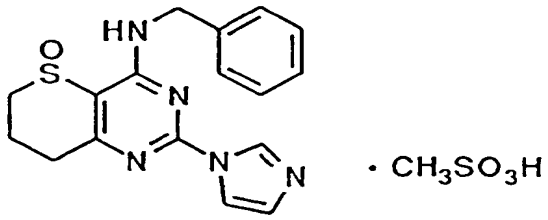


TLC: Rf 0.17 (Chloroform:Methanol=4:1);

NMR (200MHz, DMSO-d6): δ 8.44 (2H, d), 7.28 (2H, d), 7.28 (1H, brt), 4.50 (2H, d), 4.25 (2H, d), 3.47 (2H, s), 2.85-2.64 (6H, m), 2.30 (1H, m), 1.70-1.58 (2H, m), 1.35-1.15 (2H, m).

IR (KBr): ν 3368, 2922, 1654, 1626, 1562, 1491, 1420, 1360, 1235, 1033, 953, 782, 756 cm^{-1}.

Example 5



To a solution of the compound prepared in Example 2(3) (0.245 g) in dichloromethane (5 mL) was added a solution of 3-chloroperoxybenzoic acid (0.196 g) in dichloromethane (2 mL) at -10 °C under an atmosphere of argon gas. The mixture was stirred at same temperature for 10 min. The mixture was quenched by addition of a saturated aqueous solution of ammonium chloride, extracted with dichloromethane. The extract was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography (dichloromethane:methanol=49:1) to give the title compound (0.163g) having the following physical data. (free base)

TLC: Rf 0.23 (Dichloromethane:Methanol=19:1);

NMR (200MHz, DMSO-d6): δ 8.80 (1H, t), 8.40 (1H, s), 7.78 (1H, s), 7.42-7.18 (5H, m), 7.02 (1H, s), 4.70 (2H, d), 3.20 (1H, m), 3.10-2.80 (3H, m), 2.40 (1H, m), 2.08 (1H, m).

(CH_3SO_3H salt)

TLC: Rf 0.34 (Dichloromethane:Methanol=19:1);

NMR (200MHz, DMSO-d6): δ 9.73 (1H, s), 9.07 (1H, t), 8.23 (1H, s), 7.77 (1H, s), 7.46-7.20 (5H, m), 4.85 (1H, dd), 4.75 (1H, dd), 3.38-3.20 (1H, m), 3.12-2.95 (1H, m), 2.88-2.80 (2H, m), 2.50-2.30 (1H, m), 2.35 (3H, s), 2.20-2.00 (1H, m);

IR (KBr): ν 3401, 1603, 1515, 1445, 1407, 1349. 1194, 1059, 1032, 884, 785, 705, 623, 563, 537 cm^{-1}.

Example 5(1) and 5(2)

The following compounds were obtained by the same procedure as Example 5, by using the corresponding compound prepared by Example 2(5) or 2(6) instead of the compound prepared in Example 2(3).

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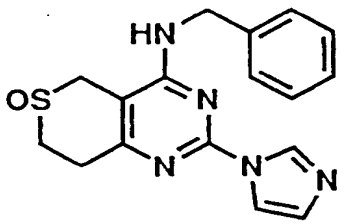
Example 5(1)



· CH_3SO_3H

(free base)

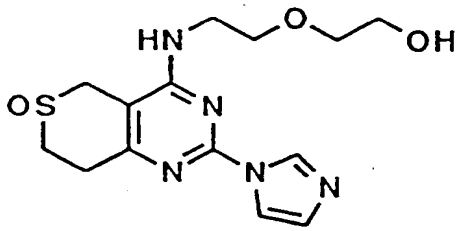
TLC: Rf 0.50 (Chloroform:Methanol=7:1);

NMR (200MHz, DMSO-d6): δ 8.39 (1H, s), 8.07 (1H, t), 7.77 (1H, s), 7.44-7.15 (5H, m), 7.03 (1H, s), 4.66 (2H, d), 3.80 (2H, s), 3.29-2.80 (4H. m). (CH_3SO_3H salt)

NMR (200MHz, DMSO-d6): δ 9.82 (1H, s), 8.37 (1H, t), 8.27 (1H, s), 7.82 (1H, s), 7.48-7.18 (5H, m), 4.76 (2H, d), 3.84 (2H, s), 3.35-2.85 (4H, s), 2.35 (3H, s).

IR (KBr): ν 3435, 3257, 3167, 1612, 1573, 1542, 1522, 1441,1411, 1392, 1350, 1197, 1060, 1043, 893, 829, 785, 774, 751, 705, 623, 563, 537, 506 cm^{-1}.

Example 5(2)

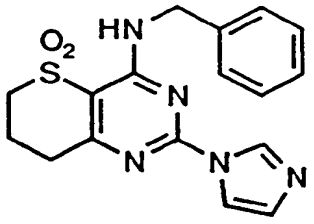


TLC: Rf 0.28 (Chloroform:Methanol=8:1);

NMR (200MHz, DMSO-d6): δ 8.46 (1H, s), 7.83 (1H, s), 7.58-7.38 (1H, br), 7.06 (1H, s), 4.70-4.53 (1H, br), 3.90-2.80 (14H, m);

IR (KBr): ν 3401, 2930, 1603, 1536, 1479, 1450, 1342, 1201, 1120, 1057, 1026, 834, 752, 656, 613 cm^{-1}.

Example 6



· CH_3SO_3H

To a solution of the compound prepared in Example 2(3) (0.152 g) in dichloromethane (3 mL) was added a solution of 70% 3-chloroperoxybenzoic acid (0.238 g) in dichloromethane (3 mL) at 0 °C under an atmosphere of argon gas. The mixture was stirred at same temperature for 2 hours and at room temperature for 3 hours. The mixture was

BNSDOCID: <EP___0728759A1_I_>

quenched by addition of a saturated aqueous solution of ammonium chloride, extracted with dichloromethane. The extract was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography (dichloromethane:methanol=19:1) to give the title compound (0.168g) having the following physical data.

(free base)

TLC: Rf 0.59 (Dichloromethane:Methanol=19:1);

NMR (200MHz, DMSO-d6): δ 8.40 (1H, s), 8.10 (1H, t), 7.78 (1H, s), 7.40-7.20 (5H, m), 7.05 (1H, s), 4.78 (2H, d), 3.60 (2H, m), 2.90 (2H, m), 2.30 (2H, m).

(CH_3SO_3H salt)

TLC: Rf 0.43 (Dichloromethane:Methanol=19:1).

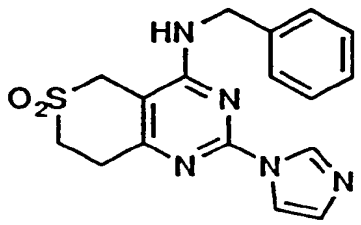
NMR (200 MHz, DMSO-d6): δ 9.68 (1H, s), 8.28 (1H, t), 8.20 (1H, s), 7.75 (1H, s), 7.45-7.20 (5H, m), 4.86 (2H, d), 3.71-3.65 (2H, m), 3.02-2.92 (2H, m), 2.40-2.22 (2H, m), 2.36 (3H, s);

IR (KBr): ν 3436, 1611, 1524, 1450, 1412, 1274, 1210, 1051, 761, 704 cm^{-1}.

Example 6(1) and 6(2)

The following compounds were obtained by the same procedure as Example 6, by using the corresponding compound prepared by Example 2(5) or 2(6) instead of the compound prepared in Example 2(3).

Example 6(1)



· CH_3SO_3H

(free base)

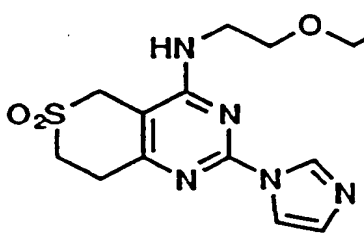
TLC: Rf 0.62 (Chloroform:Methanol=7:1);

NMR (200MHz, DMSO-d6): δ 8.40 (1H, s), 8.15-8.03 (1H, m), 7.77 (1H, s), 7.45-7.15 (5H, m), 7.04 (1H, s) 4.66 (2H, d), 3.54 (2H, t), 3.20 (2H, t). (CH_3SO_3H salt)

NMR (200MHz, DMSO-d6): δ 9.80 (1H, s), 8.43-8.23 (2H, m), 7.81 (1H, s), 7.48-7.18 (5H, m), 4.76 (2H, d), 4.27 (2H, s), 3.59 (2H, t), 3.26 (2H, t), 2.35 (3H, s).

IR (KBr): ν 3436, 3259, 3141, 1614, 1543, 1524, 1450, 1397, 1353, 1324, 1289, 1209, 1131, 1114, 1060, 902, 776, 702, 626, 555, 445 cm^{-1}.

Example 6(2)



· CH_3SO_3H

BNSDOCID: <EP___0728759A1_I_>

(free base)

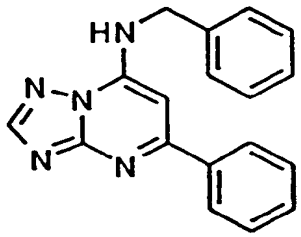
TLC: Rf 0.44 (Chloroform:Methanol=8:1);

NMR (200MHz, DMSO-d6): δ 8.47 (1H, s), 7.83 (1H, s), 7.55-7.43 (1H, m), 7.07 (1H, s), 4.63-4.55 (1H, m), 4.15 (2H, s), 3.70-3.13 (12H, m). (CH_3SO_3H salt)

NMR (200MHz, DMSO-d6): δ 9.79 (1H, s), 8.30-8.25 (1H, m), 7.85-7.73 (2H, m), 4.21 (2H, s), 3.25 (2H, t), 3.78-3.43 (10H, m), 2.33 (3H, s);

IR (KBr): ν 3410, 3275, 3144, 2969, 1615, 1523, 1449, 1392, 1349, 1323, 1287, 1209, 1193, 1118, 1053, 866, 786, 619, 563, 444 cm^{-1}.

Example 7



A mixture of the compound prepared in Reference example 14 (0.48 g) and benzylamine (0.42 g) in 30 mL of ethanol was heated at reflux for 18 hours. The mixture was then concentrated. The concentrate was treated with potassium carbonate solution and extracted with methylene chloride. The organic extract was dried over anhydrous magnesium sulfate and concentrated. The concentrate was triturated in ether and collected to give the title compound (0.5 g) having the following physical data.

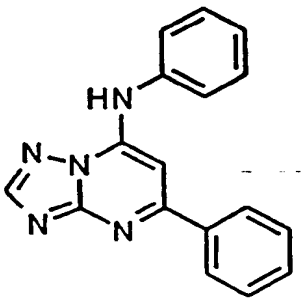
MP : 151 °C;

NMR (200MHz, $CDCl_3$): δ 4.72 (d, 2H), 6.59 (s, 1H), 7.30-7.52 (m, 8H), 8.02-8.12 (m, 2H), 8.35 (s, 1H).

Example 7(1) and 7(2)

The following compounds were obtained by the same procedure as Example 7, by using the corresponding amine instead of benzylamine.

Example 7(1)

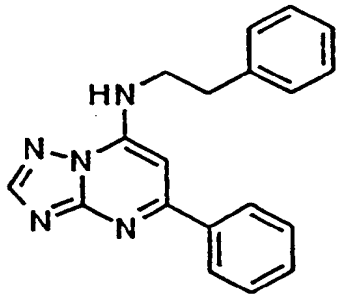


MP : 217-220 °C;

NMR (200MHz, $CDCl_3$): δ 6.97 (s, 1H), 7.32-7.60 (m, 8H), 7.90 (s, 1H), 8.12-8.15 (m, 2H), 8.44 (s, 1H).

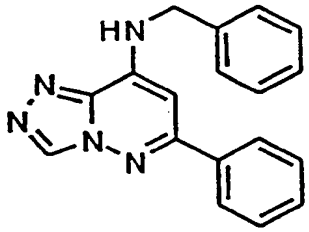
BNSDOCID: <EP___0728759A1_I_>

Example 7(2)



MP : 163-165 °C;
NMR (200MHz, $CDCl_3$): δ 3.10 (t, 2H), 3.77 (t, 2H), 6.26 (t, 1H), 6.52 (s, 1H), 7.23-7.43 (m, 5H), 7.49 (m, 3H), 8.10 (m, 2H), 8.32 (s, 1H).

Example 8



The following compounds were obtained by the same procedure as Example 7, by using the corresponding compound prepared in Reference example 15 instead of the compound prepared in Reference example 14.
MP : 276-278 °C;
NMR (200MHz, $CDCl_3$): δ 4.75 (d, 2H), 6.32 (s, 1H), 7.25-7.57 (m, 8H), 7.82 (m, 2H), 8.99 (s, 1H).

Formulation Example 1

The following components were admixed in conventional method and punched out to obtain 100 tablets each containing 50 mg of active ingredient.

4-benzylamino-2-(1-imidazolyl)-5-methylthieno[2,3-d]pyrimidine dihydrochloride (Example 2)	--- 5.0 g
cellulose calcium glycolate (disintegrating agent)	--- 0.2 g
magnesium stearate (lubricating agent)	--- 0.1 g
micro crystalline cellulose	--- 4.7 g

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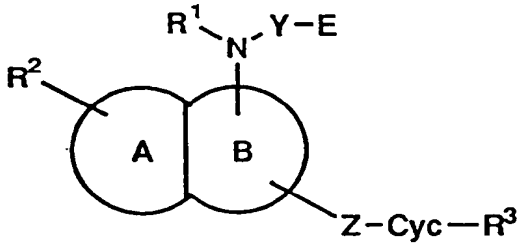
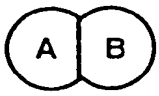
Claims

1. A heterocyclic compound of the formula (I):

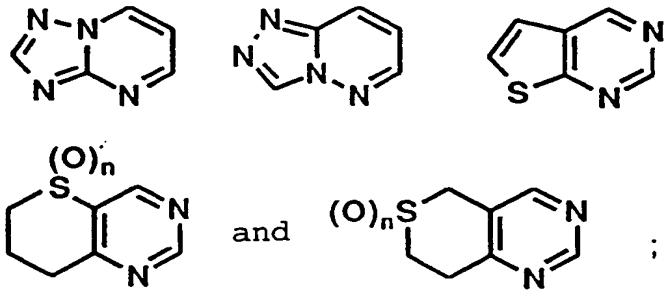


(I)

wherein



is a heterocycle selected from



n is 0, 1 or 2;
Y is single bond or C1-6 alkylene;
Z is single bond, C1-2 alkylene or vinylene;
E is

(i) 4-15 membered, unsaturated, partially saturated or fully saturated, mono or bicyclic hetero ring containing one or two hetero atoms, chosen from nitrogen, oxygen and sulfur, not more than one hetero atom being sulfur,
(ii) 4-15 membered, unsaturated or partially saturated, mono or bicyclic carbocyclic ring, or
(iii) $-OR^4$; in which R^4 is hydrogen atom, C1-4 alkyl or C1-4 alkyl substituted by a hydroxy group;

Cyc is 5-7 membered, unsaturated, partially saturated or fully saturated, monocyclic hetero ring containing one or two nitrogen atoms or 5-7 membered, unsaturated or partially saturated, monocyclic carbocyclic ring;
R^1 is hydrogen atom or C1-4 alkyl;
R^2 is hydrogen atom, C1-4 alkyl, C1-4 alkoxy or halogen atom;
R^3 is hydrogen atom, C1-4 alkyl, C1-4 alkoxy or $-COOR^5$; in which R^5 is hydrogen atom or C1-4 alkyl;
with the proviso that

(1) a Cyc ring does not bond to Z through a nitrogen atom in the Cyc ring where Z is vinylene and that
(2) Y is not a single bond, when E is $-OR^4$; or a pharmaceutically acceptable acid addition salt, pharmaceutically acceptable salt or hydrate thereof.

BNSDOCID: <EP___0728759A1_I_>

2. A compound according to claim 1 wherein Y is single bond, methylene or ethylene.

3. A compound according to claim 1 or 2 wherein Z is single bond.

4. A compound according to any one of claims 1 to 3 wherein E is pyridinyl, benzodioxanyl, phenyl, methoxy or hydroxyethoxy.

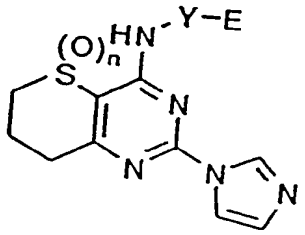
5. A compound according to any one of claims 1 to 4 wherein Cyc is imidazolyl, piperidinyl or phenyl.

6. A compound according to any one of claims 1 to 5 wherein R^1 is hydrogen.

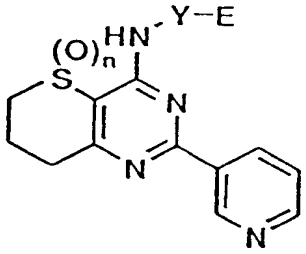
7. A compound according to any one of claims 1 to 6 wherein R^2 is hydrogen or methyl.

8. A compound according to any one of claims 1 to 7 wherein R^3 is carboxy or ethoxycarbonyl.

9. A compound according to any one of claims 1 to 8 which is of formula (IA), (IB), (IC), (ID), (IE), (IF), (IG), (IH), (IJ), (IK), (IL), (IM), (IN) or (IO):



(IA)



(IB)

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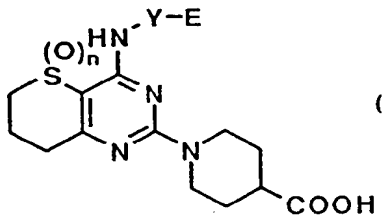
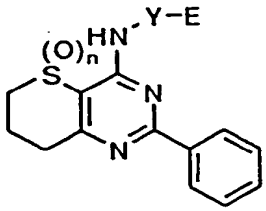
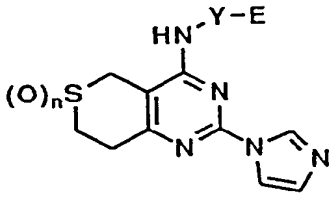


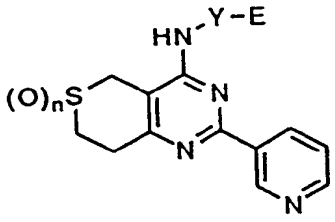
(IC)



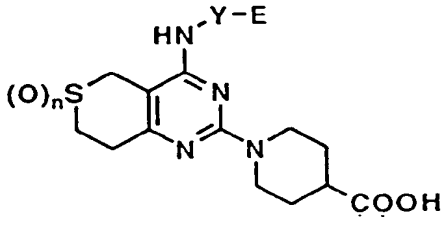
(ID)



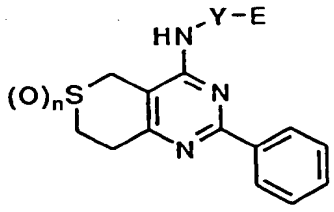
(IE)



(IF)



(IG)



(IH)

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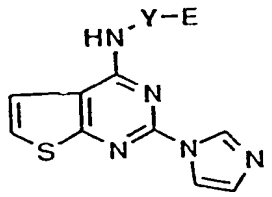
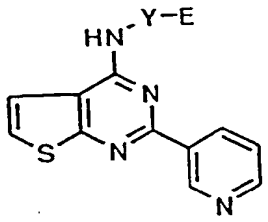
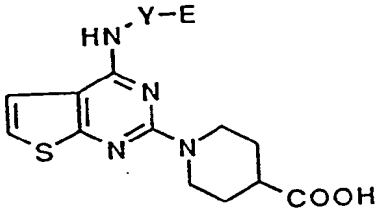


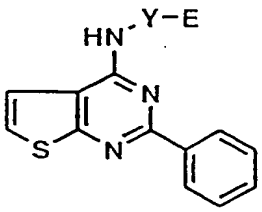
(IJ)



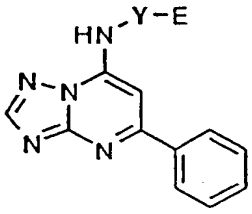
(IK)



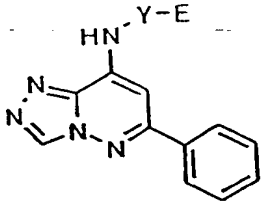
(IL)



(IM)



(IN)



(IO).

10. A compound according to any one of claims 1 to 9 which is:

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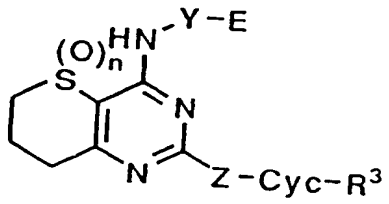
(i) a compound of formula

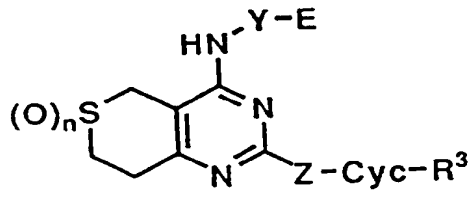


wherein

Y is methylene, E is phenyl, Z is single bond, Cyc is 1-imidazolyl, R^3 is hydrogen atom and n is 0, 1 or 2; or

Y is ethylene, E is 2-hydroxyethoxy, Z is single bond, Cyc is 1-imidazolyl, R^3 is hydrogen atom and n is 0;

(ii) a compound of formula



wherein

Y is methylene, E is phenyl, Z is single bond, Cyc is 1-imidazolyl, R^3 is hydrogen atom and n is 0, 1 or 2;

Y is ethylene, E is 2-hydroxyethoxy, Z is single bond, Cyc is 1-imidazolyl, R^3 is hydrogen atom and n is 0, 1 or 2;

Y is methylene, E is 1,3-benzodioxan-5-yl, Z is single bond, Cyc is 1-imidazolyl, R^3 is hydrogen atom and n is 0;

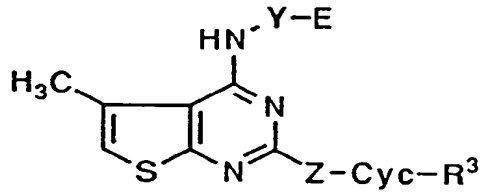
Y is methylene, E is 1,3-benzodioxan-5-yl, Z is single bond, Cyc-R^3 is 4-ethoxycarbonylpiperidinyl and n is 0;

Y is methylene, E is 1,3-benzodioxan-5-yl, Z is single bond, Cyc-R^3 is 4-carboxypiperidinyl and n is 0;

Y is methylene, E is 3-pyridinyl, Z is single bond, Cyc-R^3 is 4-carboxypiperidinyl and n is 0; or

Y is methylene, E is 4-pyridinyl, Z is single bond, Cyc-R^3 is 4-carboxypiperidinyl and n is 0;

(iii) a compound of formula



wherein

Y is methylene, E is phenyl, Z is single bond, Cyc is 1-imidazolyl and R^3 is hydrogen atom;

Y is ethylene, E is methoxy, Z is single bond, Cyc is 1-imidazolyl and R^3 is hydrogen atom; or

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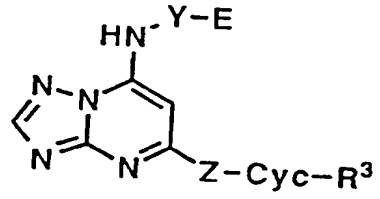
(iv) a compound of formula



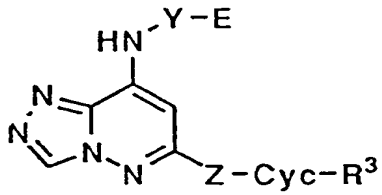
wherein

Y is methylene, E is phenyl, Z is single bond, Cyc is phenyl and R^3 is hydrogen atom;

Y is single bond, E is phenyl, Z is single bond, Cyc is phenyl and R^3 is hydrogen atom; or

Y is ethylene, E is phenyl, Z is single bond, Cyc is phenyl and R^3 is hydrogen atom; or

(v) a compound of formula



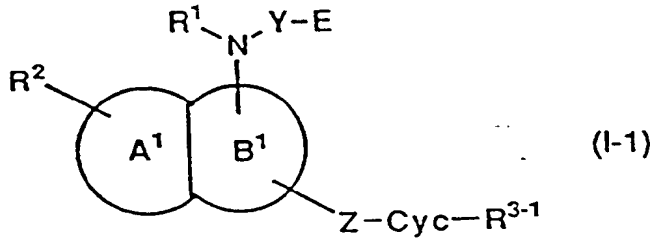
wherein

Y is methylene, E is phenyl, Z is single bond, Cyc is phenyl and R^3 is hydrogen atom;

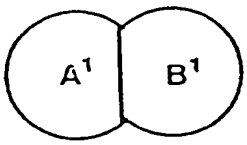
or a pharmaceutically acceptable acid addition salt, pharmaceutically acceptable salt or hydrate thereof.

11. A process for the preparation of a compound of formula (I) according to any one of claims 1 to 10 or a pharmaceutically acceptable acid addition salt, pharmaceutically acceptable salt or hydrate thereof, which process comprises:

(i) when the compound of formula (I) is of formula (I-1).



(I-1)



wherein is selected from

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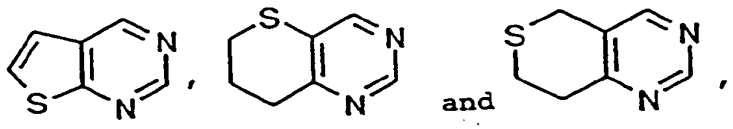
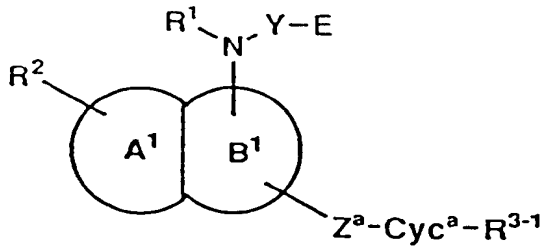


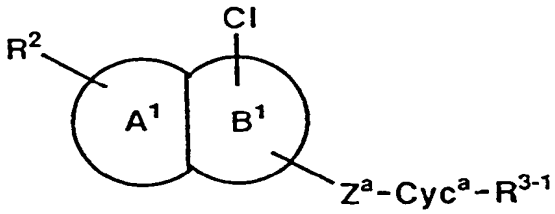
R^{3-1} is as defined in claim 1 for R^3 except that R^{3-1} does not represent a COOH group, and the other symbols are as defined in claim 1, any one of the following methods (a) to (c):

(a) when the compound of formula (I-1) is of formula (I-a)



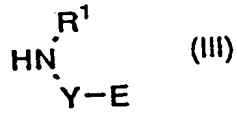
(I-a)

wherein Z^a is as hereinbefore defined for Z and Cyc^a is as hereinbefore defined for Cyc, provided that Z^a is bonded directly to a carbon atom in the ring represented by Cyc^a, and the other symbols are as hereinbefore defined,
reacting a compound of the formula (II-a)



(II-a)

wherein all symbols are as hereinbefore defined, with an amine of the formula (III)



(III)

wherein all symbols are as hereinbefore defined;

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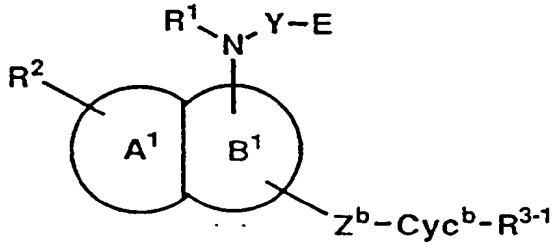
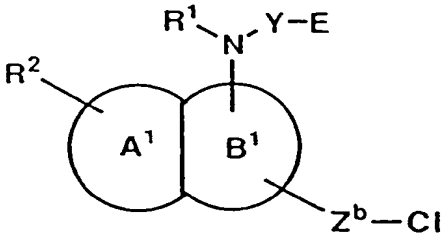
(b) when the compound of formula (I-1) is of formula (I-b)



(I-b)

wherein Z^b is single bond or methylene and Cyc^b is as hereinbefore defined for Cyc, provided that Z^b is bonded directly to a nitrogen atom in the ring represented by Cyc^b, and the other symbols are as hereinbefore defined, reacting a compound of the formula (II-b)

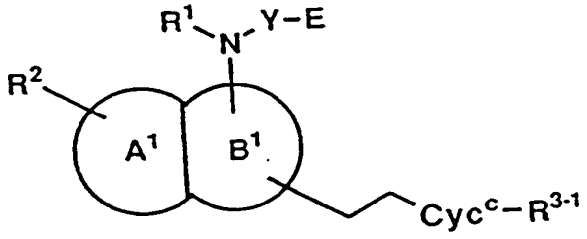


(II-b)

wherein all symbols are as hereinbefore defined, with a heterocyclic amine of the formula (IV)

$$H—Cyc^b\text{-}R^{3\text{-}1} \qquad (IV)$$

wherein all symbols are as hereinbefore defined;
(c) when the compound of formula (I-1) is of formula (I-c)



(I-c)

wherein Cyc^c is as hereinbefore defined for Cyc, provided that ethylene is bonded directly to a nitrogen atom in the ring represented by Cyc^c, and the other symbols are as hereinbefore defined,
reacting a compound of the formula (II-c)

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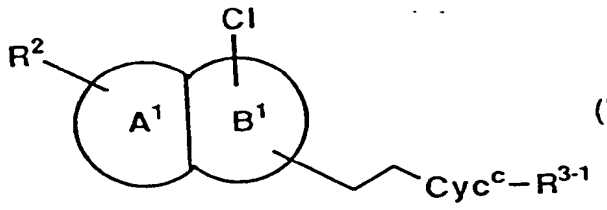
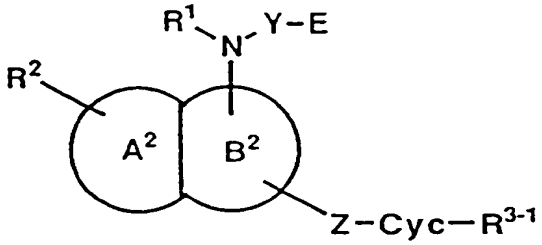


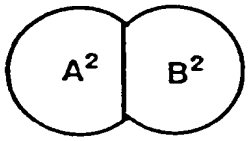
(II-c)

wherein all symbols are as hereinbefore defined, with an amine of the formula (III);
(ii) when the compound of formula (I) is of formula (I-2)

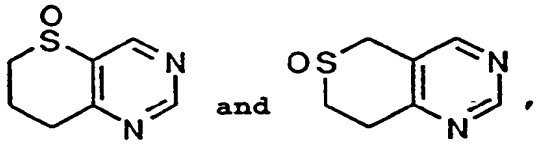


(I-2)

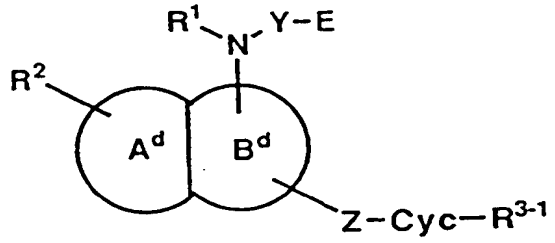
wherein



is selected from



and the other symbols are as defined in claim 1, oxidation of a corresponding compound having a sulfide group of formula (I-d)



(I-d)

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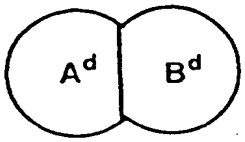
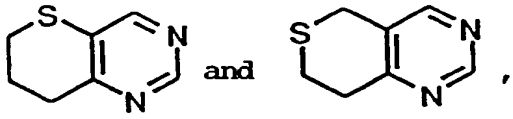
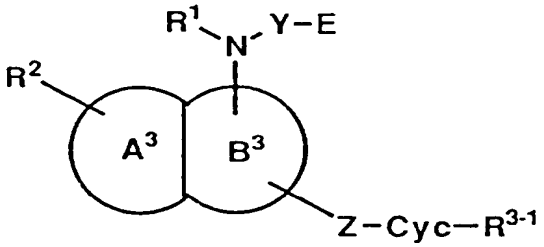
wherein



is selected from

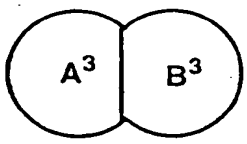


and the other symbols are as hereinbefore defined;
(iii) when the compound of formula (I) is of formula (I-3)

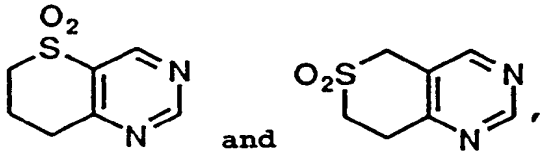


(I-3)

wherein



is selected from



and the other symbols are as defined in claim 1, oxidation of a corresponding compound having a sulfide group of formula (I-d), or oxidation of a corresponding compound having a sulfinyl group of formula (I-2);

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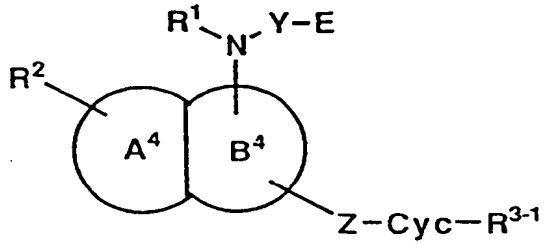
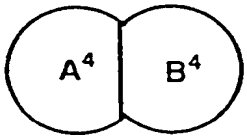
(iv) when the compound of formula (I) is of formula (I-4)

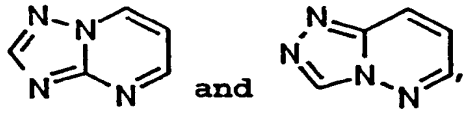


(I-4)

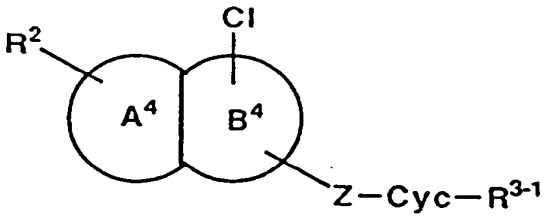
wherein



is selected from



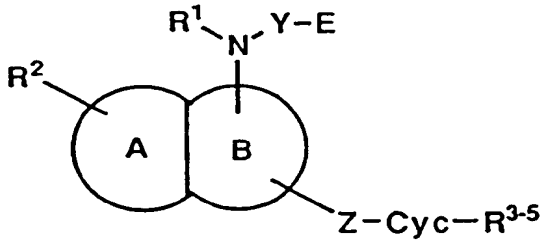
and the other symbols are as defined in claim 1, reacting a compound of formula (II-d)



(II-d)

wherein all symbols are as hereinbefore defined, with an amine of formula (III); or

(v) when the compound of formula (I) is of formula (I-5)



(I-5)

wherein R^{3-5} represents a COOH group, and the other symbols are as defined in claim 1,

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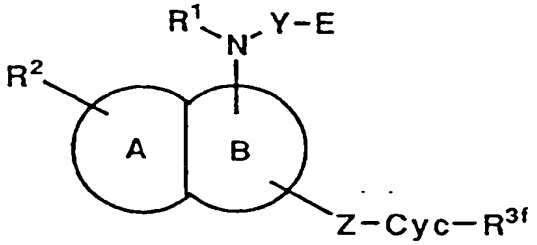
hydrolysis of a compound of formula (I-1), (I-2), (I-3) or (I-4) having an ester group, i.e., a compound of formula (I-f)



(I-f)

wherein R^{3f} represents $COOR^{5f}$ in which R^{5f} represents C1-4 alkyl, and the other symbols are as hereinbefore defined;

optionally followed by the conversion of the compound of formula (I) thus obtained into an acid addition salt, salt or hydrate.

12. A pharmaceutical composition which comprises, as active ingredient, a compound of formula (I) according to any one of claims 1 to 10 or a pharmaceutically acceptable acid addition salt, pharmaceutically acceptable salt or hydrate thereof; and a pharmaceutically acceptable carrier.

13. Use of a compound of formula (I) according to any one of claims 1 to 10 or a pharmaceutically acceptable acid addition salt, pharmaceutically acceptable salt or hydrate thereof for use in the manufacture of a medicament for the prevention or treatment of hypertension, heart failure, myocardial infarction, angina, atherosclerosis, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, asthma, bronchitis, dementia, immunodeficiency, pulmonary hypertension, inflammation, thrombosis, cerebral apoplexy, cardiostenosis or cerebral infarction.

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European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 96 30 1223

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	EP-A-0 082 023 (SANKYO CO., LTD.) * page 2, line 17 - page 3, line 2; claims 1,6,7,22 * ---	1,12,13	C07D487/04 C07D495/04 A61K31/505 A61K31/50 //(C07D487/04, 249:00, 239:00), (C07D487/04, 249:00, 237:00), (C07D495/04, 333:00, 239:00), (C07D495/04, 335:00,239:00)
X	GB-A-2 157 684 (VEB DEUTSCHES HYDRIERWERK RODLEBEN) * claims 1,11,13,14 * ---	1,12,13	
X	DD-A-99 794 (E. TENOR ET AL.) * page 1 - page 2, line 20 * ---	1,12,13	
X	FR-A-2 522 000 (MARUKO SEIYAKU CO., LTD.) * page 1, line 15 - line 21; claims 1,10,11; example 29 * ---	1,12,13	
D,X	CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 34, no. 10, 1986, pages 4150-65, XP000196068 S. OHNO ET AL.: "Synthesis and Hypoglycemic Activity of 7,8-Dihydro-6H-thiopyrano[3,2-d]pyrimidine Derivatives and Related Compounds" * page 4150, abstract; page 4152, table II, compounds 7i and 8f * ---	1,12,13	TECHNICAL FIELDS SEARCHED (Int.Cl.6) C07D
X	EP-A-0 447 891 (BASF AG) * page 29, compounds 519 to 524 * ---	1	
X	BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE, no. 3-4 (2), 1975, pages 815-9, XP000571656 J. BOURGUIGNON ET AL.: "Synthèses de thiéno[2,3-d]pyrimidines substituées en 2 et 4" * page 815, right-hand column, formulae 6b and 6c; page 818, left-hand column, paragraph 6, especially 6b and 6c * --- -/--	1	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	14 June 1996	Hass, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 96 30 1223

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE, no. 11-12 (2), 1975, pages 2483-7, XP000571654 J. BOURGUIGNON ET AL.: "Synthèses de thiéno[2,3-d]pyrimidines substituées en 2 et 4 II" * page 2483, left-hand column, second formula; right-hand column, formula 6b; page 2486, right-hand column, paragraph 6b *	1	
X	EP-A-0 452 002 (DOWELANCO) * claims 1,2 *	1	
X	US-A-4 196 207 (L.G. WEBBER) * columns 7, 8, compound 182 * * column 2, line 15 - line 40 *	1	
D,X	US-A-4 146 716 (J.M. COX ET AL.) * columns 7, 8, compound 182 *	1	
D,Y	EP-A-0 579 496 (ONO PHARMACEUTICAL CO., LTD.) * page 17, line 4 - page 19, line 26; claims 1,9,10 *	1,12,13	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
Y	EP-A-0 607 439 (EISAI CO., LTD.) * page 33, line 39 - page 39, line 59; claims 1,2; examples *	1,12,13	
D	& WO-A-93 07124		

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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	14 June 1996	Hass, C

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EUROPEAN SEARCH REPORT

Application Number
EP 96 30 1223

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Y	PHARMAZIE, vol. 42, no. 9, 1987, pages 613-6, XP000571649 P. MENTZ ET A.: "Thromboxan A2-antagonistische Wirkung von antianginösen Pharmaka unter besonderer Berücksichtigung von Trapidil und Trapidilderivaten" * page 614, right-hand column, compounds 11, 12, 13 *	1,12,13	
Y	DD-A-297 061 (MARTIN-LUTHER-UNIVERSITÄT HALLE) * claim 1 *	1,12,13	
A,D	WO-A-94 22855 (EISAI CO., LTD.) * claims 1-17 *	1,12,13	
A	EP-A-0 347 146 (SMITH KLINE & FRENCH LABORATORIES LTD.) * page 10, line 30 - page 11, line 31; claims 1,17 *	1,12,13	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
D	& US-A-5 047 404		
A	EP-A-0 248 413 (MERRELL DOW PHARMACEUTICALS INC.) * claims 1,9-11 *	1,12,13	
A	EP-A-0 441 339 (MERRELL DOW PHARMACEUTICALS INC.) * claims 1,7-12 *	1,12,13	
A	DE-C-12 51 765 (DR. K. THOMAE GMBH) * columns 4, 7, 8 *	1,12,13	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	14 June 1996	Hass, C

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X : particularly relevant if taken alone
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